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# **BMJ Open**

### Evaluating transportability of overall survival estimates from US to UK populations receiving first-line treatment for advanced non-small cell lung cancer: a retrospective cohort study

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Evaluating transportability of overall survival estimates from US to UK populations receiving first-line treatment for advanced non-small cell lung cancer: a retrospective cohort study Seamus Kent, PhD<sup>1\*</sup>, Philani Mpofu, PhD<sup>2\*</sup>, Stephen Duffield, MD, PhD<sup>3</sup>, Jane Adam, FRCR<sup>3</sup>, Brennan Beal, PharmD<sup>2</sup>, Trevor J. Royce, MD, MPH<sup>2</sup>, Blythe Adamson, PhD, MPH<sup>2,4</sup>, Jyotsna Kasturi, PhD<sup>2</sup>, Arun Sujenthiran, MD<sup>1</sup>, Páll Jónsson, PhD<sup>3</sup> \*Drs Kent and Mpofu contributed equally to this work <sup>1</sup>Flatiron Health UK Ltd, London, UK <sup>2</sup>Flatiron Health, Inc, New York, NY, USA <sup>3</sup>National Institute for Health and Care Excellence, Manchester, UK <sup>4</sup>The Comparative Health Outcomes, Policy and Economics (CHOICE) Institute, University of Washington, Seattle, WA, USA Corresponding Author: Philani Mpofu, PhD, Flatiron Health, 233 Spring Street, New York, NY, 10013; philani.mpofu@flatiron.com Word count: 3353/4000 1 Figure/2 Tables Keywords: Transportability; MAIC; aNSCLC; overall survival For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 

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1 ว		2
2 3 4	23	ABSTRACT
5	24	
7 8	25	Objectives: To explore how the United Kingdom (UK) versus the United States (US) compare in
9 10	26	patient characteristics, treatment patterns, and overall survival (OS) of patients with advanced
11 12	27	non-small cell lung cancer (aNSCLC) initiating first-line (1L) treatment.
13 14	28	Design: Retrospective cohort study
15 16	29	Setting: Oncology treatment centres in the US and UK
17 18 10	30	Participants: People in the US and UK diagnosed with aNSCLC, and treated in the 1L setting
19 20 21	31	between 2016–2018. The US cohort was obtained from a nationwide electronic health record
22 23	32	(EHR)-derived de-identified database. The UK cohort information was derived from a published
24 25	33	study exploring the patient characteristics, treatments, and outcomes of people with aNSCLC in
26 27	34	the UK.
28 29	35	Interventions: 1L chemotherapy, immunotherapy monotherapy, or targeted therapy.
30 31	36	Primary and secondary outcome measures: The primary outcome was overall survival (OS)—
32 33	37	defined as the time from treatment initiation to death from any cause.
34 35 26	38	Results: There were 1003 patients in the UK and 3819 in the US cohorts receiving 1L therapy
30 37 38	39	for aNSCLC. After standardising the US cohort to the UK cohort, median OS in the US and UK
39 40	40	was similar across 1L drug classes: chemotherapies (7.7 [95% CI 7.1–8.3] vs. 8.1 [95% CI 7.4–
41 42	41	8.9] months), immunotherapies (13.9 [95% CI 11.0–17.1] vs. 14.0 [95% CI 10.7–20.6]), and
43 44	42	targeted therapies (21.6 [95% CI 18.5-23.7] vs. 20.2 [95% CI 16.0-30.5]). OS curves for 1L
45 46	43	immunotherapy and targeted therapy were almost overlapping after standardisation. OS after
47 48	44	around 12 months was higher in US patients compared to UK patients receiving 1L chemotherapy
49 50	45	regimens. Of those receiving 1L chemotherapy, the proportion receiving any second-line therapy
51 52 53 54 55 56	46	appeared higher for patients in the US vs. UK.

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47 Conclusions: The results suggest that in aNSCLC patients receiving 1L treatment, US data has
48 potential to be used in technology evaluations to understand long-term OS where UK data is
49 unavailable or sparse.

## 51 STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first observational study to assess the comparability of overall survival among
   people with aNSCLC in the UK versus the US after standardising the US population to the
   UK population.
- 55 The study exemplifies the simple methodology that can be employed to generate empirical
   56 evidence that can help HTA bodies in assessing the applicability of international evidence
   57 to local decision-making.
- 58 ... Limitations include that the patient-level data were not available in the UK, as a result, we
   59 used summary statistics from a recent publication in the UK. The use of a published article
   60 not only limited the variables on which we could standardise but also limited the
   61 population-adjustment methodology that could be used.
- 62 The population-adjustment was limited to patient demographic and clinical characteristics,
   63 and did not include other factors that can influence transportability, for example,
   64 differences in healthcare systems across countries.

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#### 65 INTRODUCTION

Health technology assessment bodies require evidence on a wide and varied number of questions to inform pricing and reimbursement decisions. Common evidence types include the characteristics of the target population, natural history of disease, diagnostic and treatment patterns, use of medicines including time-on-treatment, long-term outcomes like overall survival and event rates, resource use and costs, quality of life, and the causal effects of treatment. For questions other than causal effects of treatments, real-world data is the preferred source of evidence.[1] Because the evidence must be relevant to patients treated in a given healthcare system, HTA bodies typically indicate a preference for local data.[1–3] Unfortunately, local data may not always be available or sufficient to answer all questions of interest. This is especially true where the target population is small, such as in patients expressing a rare biomarker or tumour type, where sharing of evidence across countries may be necessary to achieve sufficient statistical power.

Given that the availability of data varies across countries, it is important to understand when and how evidence from one country can be utilised to fill evidence gaps in another. Manufacturers are increasingly submitting international data to HTA bodies as part of their evidence dossiers. The most common use case beyond comparative effectiveness has been to provide data on long-term outcomes, usually overall survival but also progression-free survival and time-on-treatment, for the local standard of care to inform extrapolation and costs in economic models. Assumptions about long-term outcomes and time-on-treatment are recognised to be key drivers of cost-effectiveness but are usually subject to substantial uncertainty based on trial data alone due to limited follow-up and questions about the relevance of the trial population to the decision.[4]

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Where international data has been presented, there has been variation in its acceptance across HTA bodies but also across evaluations within HTA bodies.[5] Decision making committees are uncertain how to value international data given the differences between countries in terms of populations, healthcare systems and access, and clinical practice. This is expected to be a greater challenge for absolute outcomes than for comparative outcomes like relative treatment effects.[6] While informative general frameworks for considering transportability—that is, extending evidence beyond the population used in evidence generation—have been developed,[7] they are limited in their ability to guide specific decisions. For this, empirical studies on the transportability of evidence across countries is valuable; however, few such studies are currently available. One recent study found overall survival to be similar in patients receiving first-line (1L) chemotherapy or immunotherapies for advanced non-small cell lung cancer (aNSCLC) in the US and Alberta, Canada after adjusting for baseline patient demographic and clinical characteristics.[8] In this study, we aim to explore the transportability from the US to the UK of estimates of overall survival and time-on-treatment for patients receiving different classes of drugs for 1L treatment of aNSCLC. **METHODS** Data sources In the absence of available individual patient-level data from the UK, we performed a pragmatic literature review to identify studies reporting outcomes for patients with aNSCLC in the UK (Supplementary Table 1). We prioritised studies that had broad population coverage, reflected current treatment practices (since the emergence of immunotherapies), and reported overall survival or time-on-treatment by treatment class. We identified three candidate studies[9–11] and selected Lester et al. 2021 for our primary analysis because it was a multicentre study reporting

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detailed outcomes data by 1L drug class.[9] We used Pilleron et al. 2023 for sensitivity analysis.[10] Pilleron et al. presented population level data from the national UK Systemic Anti-Cancer Treatment (SACT) registry but only for patients receiving 1L chemotherapy regimens. We excluded Snee et al. 2021 because the study did not describe the patient characteristics of patients with advanced disease and outcomes were reported from diagnosis rather than initiation of treatment.[11]

Data for patients treated in the United States came from the nationwide electronic health record (EHR)-derived, de-identified Flatiron Health database—a longitudinal database comprising structured and unstructured data curated using technology enabled human abstraction.[12] At the time of this study, de-identified patient-level data were derived from ~280 US cancer clinics (~800 sites of care) and rule-based lines of therapy were defined by expert oncology clinicians. The data processing and quality assurance procedures for Flatiron Health data are described in detail elsewhere.[13] 

#### Study population

The UK patient population was based on a retrospective real-world study that identified patients from nine UK centres who initiated 1L systemic anticancer therapy between June 1, 2016, and March 31, 2018 and had a median follow-up of 9.2 months.[9] Patients were included if they were 18 years of age or older, were diagnosed with metastatic disease, were not enrolled in a clinical trial during the study period, and were not missing relevant data (date of diagnosis, age, sex, Eastern Cooperative Oncology Group [ECOG] performance status [PS], histology, and response). We applied comparable inclusion criteria to the US data to match the population included in the UK study. We restricted analysis to patients with a lung cancer diagnosis (ICD-9 162.x or ICD-10 C34x or C39.9); at least two documented clinical visits; pathology consistent with aNSCLC that was confirmed using unstructured data; stage IV disease (confirmed using unstructured data);

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aged 18 years or older at diagnosis; treatment naive; were exposed to relevant therapies in 1L; were not enrolled in clinical trials during the study period; had no gaps between diagnosis and EHR activity exceeding 90 days to ensure more complete treatment information, and had ECOG PS recorded within 30 days of the index date. The UK EHR study did not report how they categorised combination therapies comprising more than one drug class, although such combinations are expected to be rare. We excluded patients with such combination therapies from the US cohort when categorising 1L treatment. Patients were selected for the US cohort over the same time period as the UK study. The Institutional Review Board of WCG IRB (Reference #: IRB00000533) gave ethical approval for the study protocol prior to study conduct, and included a waiver of informed consent.

#### 153 Outcomes

The study outcomes of interest were overall survival (OS) and time-to-treatment discontinuation (TTD). Overall survival was defined in both cohorts as time from initiation of 1L treatment to the date of death from any cause. Both studies have reported high sensitivity and specificity for mortality.[14,15] For the US cohort, TTD was defined as time from initiation of 1L therapy to the last drug episode for the specific drug of interest in the 1L, which is consistent with standard definitions in HTA. For the UK cohort, TTD was defined as time from initiation of 1L therapy to the start of the last cycle of therapy (which will tend to underestimate true TTD). Since TTD was defined differently between these studies, we present US TTD outcomes for completeness but do not compare them with UK TTD. UK patients were censored at the earliest of the end of the study period or the date of last assessment; US patients were censored at the earliest of the end of the study period or at the last activity recorded in the EHR. 

166 Analysis

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We compared baseline characteristics for all variables available for the UK cohort plus additional variables for the US cohort, noting differences in definitions where present, for all 1L aNSCLC treatment and by drug class (chemotherapy, immunotherapy, or targeted therapies). We also presented differences in use of second-line (2L) therapies after 1L. Comparison of 2L therapies is limited by uncertainty as to how combination therapies consisting more than one drug class were categorised in the UK cohort study.

We used matching-adjustment to weight the US patients for standardisation of baseline characteristics to be more similar to the UK patient population. Specifically, we standardised the US study population to match the average characteristics (age, sex, ECOG PS score [0–1 or 2+], and histology [squamous cell, non-squamous cell, unknown]) of patients in the UK using the matching adjusted indirect comparison approach, overall and by 1L drug class.[16] We compared OS between UK and US patients before and after standardisation, and Kaplan-Meier survival curves (KM), median survival, and restricted mean survival time (RMST) at 12 and 24 months from the index date of 1L treatment initiation. Published KM figures from the UK study were digitised and reproduced here following the algorithm from Guyot et al. 2012.[17] Our comparison is purely descriptive—we do not perform hypothesis tests of transportability because there is no established threshold for when results can be considered transportable; this will depend on the use case and decision context including the amount of decision uncertainty. To explore whether we were unable to account for important prognostic variables in our standardisation model, we modelled OS in the US cohort using Cox proportional hazards model regression conditional on 1L drug class (for the overall model only), age, sex, ECOG PS score, histology, race, year, time since diagnosis to treatment initiation, smoking history, and biomarker status (ALK, ROS1, EGFR, *PD-L1*) and compared models using likelihood ratio tests using 5% significance level.

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We performed several sensitivity analyses. First, we extended the enrollment window for US data to October 1, 2015 to reflect when immunotherapies first became available for aNSCLC in the US and repeated the primary analysis. Second, rather than excluding people with missing ECOG PS scores in the US data, we imputed ECOG PS assuming best (ECOG PS 0 or 1) and worst (ECOG PS 2+) and repeated the primary analysis. Third, we repeated the main analysis using data from Pilleron et al. (2023) for comparison. The study by Pilleron et al. included adult patients with aNSCLC treated with chemotherapy between 2014 to 2017 in the UK followed until the end of 2018 and presented results by disease stage (III, IV) and age (<= 75, >75 years). We selected US patients from the same time period and standardised the US study population to match the average characteristics of patients in stage IV in terms of age, sex, race (white, non-white), and baseline ECOG PS score. Additional details for the study by Pilleron et al. can be found in Supplementary table 1. 

Finally, we undertook a post-hoc analysis to explore the potential role of time-period effects on observed differences in outcomes for patients treated with 1L chemotherapy, hypothesising that the earlier and faster uptake of immunotherapies in the US may impact comparability. To explore this, we compared OS for patients in the UK with patients in the US receiving 1L chemotherapy regimens before the widespread availability of immunotherapies, i.e., those initiating 1L treatment between June 1, 2012, and March 31, 2014.

<sup>43</sup> 211 <sub>44</sub>

45<br/>46212Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans
 of our research.

54 216 **RESULTS** 

- 56 217

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The UK cohort included 1003 patients meeting the inclusion criteria, with 69.6%, 17.8%, and 12.6% of patients initiating chemotherapy, immunotherapy, and targeted therapy, respectively. After applying inclusion criteria, the US cohort included 3819 patients initiating 1L therapy (Supplementary Figure 1). Of these patients, 60.6%, 21.9%, and 17.5% initiated chemotherapy, immunotherapy, and targeted therapy, respectively (Table 1).

Age and sex distributions were similar in the US and UK populations regardless of 1L therapy (Table 1). The median age was 68 years (range 28–93) for UK patients and 69 years (IQR 61– 76; range 21–81) for US patients. 541 (53.9%) patients in the UK were male compared to 2013 (52.7%) in the US. Most patients in the two cohorts had ECOG PS scores of 0 or 1 (759 [75.7%] in the UK versus 2786 [73.0%] in the US). The proportion of patients with ECOG PS scores of 0 or 1 were higher in the UK compared to the US for patients initiating immunotherapies and lower for those initiating targeted therapies. The mix of lung cancer histology types differed slightly between the countries, with the proportion of patients with non-squamous cell disease being lower in the UK compared to the US cohort (641 [63.9%] versus 2684 [70.3%]), but missing data on histology was greater in the UK. Biomarker prevalence rates were not comparable due to different classifications used. Median follow-up was 9.0 months in the US versus 9.2 months in the UK but this varied substantially by 1L drug class.

A lower proportion of patients went on to receive 2L treatment in the UK compared to the US: 287 (29%) patients in the UK versus 1835 (48%) in the US (Supplementary Table 2), though this may partly be driven by differences in censoring rates and how the 2L combination therapies were classified. Excluding 2L combination therapies consisting of more than one drug class for patients in the US leads to a switching rate of 40%. This pattern is observed regardless of 1L drug class.

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Table 1. Baseline charact	teristics an	d details of	follow-up fo	r patients i	n the UK an	d US by 1L dru	iĝicless Inclue	
	Ove	erall	1L Ch	emo	1L IO m	onotherapy	ing 71 L targ	eted the
Characteristic	UK (n=1003)	US (n=3819)	UK (n= 698)	US (n=2313)	UK (n = 179)	US (n=836)	for UPK (n = ເຮ m ຊີ126)	US (n
Proportion of study pop., %	100	100	69.6	60.6	17.8	21.9	nber 212.6 es rela	17
Median follow-up (range*), months	9.2 (0.0– 42.7)	9.0 (0.0– 42.9)	7.9 (0.0– 42.7)	7.3 (0.0– 42.9)	12.7 (0.1– 37.3)	8.1 (0.0–42.3)	10023 (0.1- 10023 (0.1- 1007.1)	20.3 (0.
Median age(range*), years	68 (28–93)	69 (21–81)	68 (28–88)	69 (21–81)	67 (48–90)	71(38–81)	<b>6 8 8 6 1 1 1 1 1 1 1 1 1 1</b>	69 (2
Sex, n (%)				1311			oaded fr erieur (/ and dat	
Male	541 (53.9)	2013 (52.7)	395 (56.6)	(56.7)	94 (52.5)	439 (52.5)	<b>n (41.3</b> )	263 (
Female	462 (46.1)	1806 (47.3)	303 (43.4)	(43.3)	85 (47.5)	397 (47.5)	<b>ing</b> , · 7 <b>4</b> (58.7)	407 (
Tumour histology, n (%)							/bmj	
Squamous	243 (24.2)	957 (25.1)	202 (28.9)	730 (31.6)	38 (21.2)	210 (25.1)	aining (2.4)	17 (
Non-squamous	641(63.9)	2684 (70.3)	391 (56.0)	1460 (63.1)	133(74.3)	584 (69.9)	and 167 (92.9)	640 (
Not specified	119 (11.9)	178 (4.7)	105 (15.0)	123 (5.3)	8 (4.5)	42 (5.0)	simil	13 (
ECOG PS score, n (%)							on Ju ar te	
0–1	759 (75.7)	2786 (73.0)	513 (73.5)	1714 (74.1)	157 (87.7)	556 (66.5)	chnol 81 (70.6)	516 (
2+	244 (24.3)	1033 (27.0)	185 (26.5)	599 (25.9)	22 (12.3)	280 (33.5)	ogie: 30 (29.4)	154 (
Race/Ethnicity, No. (%)							5 at /	
Asian	••	117 (3.1)	••	35 (1.5)	••	17 (2.0)	: Agen	65 (
Black or African American	••	354 (9.3)	••	235 (10.2)	••	75 (9.0)	ce B:	44 (
		0070 (70.4)		1651		000 (70 7)	blio	

	Ove	erall	1L Ch	emo	1L IO I	nonotherapy	5 5 1 L targ	eted therapy
Characteristic	UK (n=1003)	US (n=3819)	UK (n= 698)	US (n=2313)	UK (n = 179)	US (n=836)	UK (n = ■126)	US (n=670)
Other Race	••	333 (8.7)	••	185 (8.0)	••	66 (7.9)	Dec	82 (12.2)
/lissing/Unknown	••	337 (8.8)	••	207 (8.9)	••	70 (8.4)	emb Ens	60 (9.0)
Practice Type, No. (%)							er 20 eigne	
Community	••	3241 (84.9)	••	1985 (85.8)	••	725 (86.7)	24. Do	531 (79.3)
Academic	••	521 (13.6)	••	290 (12.5)	••	104 (12.4)	Supe	127 (19.0)
Both	••	57 (1.5)	••	38 (1.6)	••	7 (0.8)	• • • •	12 (1.8)
Time from advanced diag. to treatment initiation (months)							d from htt r (ABES)	
Median (IQR)	••	1.15 (0.76– 1.74)		1.15 (0.72– 1.68)	••	1.25 (0.85–1.97)		1.12 (0.79–1.61)
Smoking History, No. (%)						2	open	
History of smoking	••	3200 (83.8)	••	2095 (90.6)	••	765 (91.5)	.bmj.	340 (50.7)
No history of smoking	••	610 (16.0)	••	213 (9.2)	••	70 (8.4)		327 (48.8)
Jnknown/Not documented	••	9 (0.2)	••	5 (0.2)	••	1 (0.1)	on .	3 (0.4)
EGFR Status, No. (%)						Č	une	
Mutation positive	108 (10.8)	556 (14.6)	1 (0.1)	65 (2.8)	0 (0.0)	11 (1.3)		480 (71.6)
Mutation negative	••	2078 (54.4)	••	1333 (57.6)	••	613 (73.3)	• • •	132 (19.7)
Jnknown/Missing	••	1185 (31.0)	••	915 (39.6)	••	212 (25.4)	: Age	58 (8.7)
ALK Status, No. (%)							nce I	
Rearrangement present	19 (1.9)	97 (2.5)	0 (0.0)	8 (0.3)	0 (0.0)	5 (0.6)	<u>照</u> 1월 (15.1)	84 (12.5)

	Ove	erall	1L Ch	emo	1L IO m	onotherapy	in Sil L targ	jeted thera
Characteristic	UK (n=1003)	US (n=3819)	UK (n= 698)	US (n=2313)	UK (n = 179)	US (n=836)	uding = 126)	US (n=
Rearrangement not present	••	2332 (61.1)		1302 (56.3)		604 (72.2)	r Decem En	426 (6
Unknown/Missing	••	1390 (36.4)	••	1003 (43.4)	••	227 (27.2)	• • • • • • • • • • • • • • • • • • •	160 (2
ROS1 Status, No. (%)							024. ated t	
Rearrangement present	••	33 (0.9)		8 (0.3) 1024		1 (0.1)	Downle	24 (3
Rearrangement not present	••	1917 (50.2)		(44.3)	••	504 (60.3)	• erieu and c	389 (5
Unknown/Missing	••	1869 (48.9)	· •	1281 (55.4)	••	331 (39.6)	: r (AB lata n	257 (3
PDL1 Status, No. (%)							n http ES)	
PD-L1 positive	182 (18.1)	388 (10.2)	3 (0.4)	149 (6.4)	179 (100)	187 (22.4)	<b>≥ 2</b> (0.0)	52 (7
<i>PD-L1</i> negative/not detected	••	709 (18.6)		513 (22.2)		40 (4.8)	: njopen.t	156 (2
Unknown/Missing	••	2722 (71.3)	••	(71.4)	••	609 (72.8)	, and .	462 (6
Cooperative Oncology Gro L1=programmed cell deat	oup perform n ligand 1. F	ance status. ROS1=ROS	EGFR=epide proto-oncoge	rmal growth	n factor recer tor tyrosine k	otor. IO=immun inase.	PD . PD /gap June 11, 2025 at Agence Bibliogra mar technologies.	L1/PD-

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Conditional on receiving 2L therapy, the proportion of people receiving immunotherapies was comparable (52% in UK versus 49% in US) but patients in the UK were more likely to receive other chemotherapy regimens (36% in UK versus 18% in US) and less likely to receive targeted therapy (12% in UK versus 16% in US). As shown in Supplementary Table 2, conditional on the 1L therapy received, there were large differences in the proportion of UK versus US patients who went on to receive 2L therapies.

The median OS across all therapies was 9.5 months (95% confidence interval [CI] 8.8-10.7) in the UK compared to 10.4 months (95% CI 9.7–11.0) in the US prior to population adjustment (standardisation) (Table 2). After population adjustment, median OS in the US (9.6 months [9.0-10.2]) was more similar to median OS in the UK, indicating the importance of matching patient characteristics across both countries. Adjusted median OS was similar in the UK and US for 1L chemotherapy (8.1 months [95% CI 7.4–8.9] in the UK versus 7.7 months [95% CI 7.1–8.3] in the US), immunotherapy (14.0 months [95% CI 10.7-20.6] in the UK versus 13.9 months [95% CI 11.0-17.1] in the US), and targeted therapy (20.2 months [95% CI 16.0-30.5] in the UK versus 21.6 months [95% CI 18.5–23.7] in the US). Similar patterns were observed for RMST at 12 and 24 months.

OS curves exhibited a similar shape for each 1L drug class over the duration of follow-up (Figure 1). In general, the OS curves were similar and overlapping in all treatment groups once the data was adjusted to match patient characteristics. For 1L chemotherapy—irrespective of adjustment (standardisation)—the OS curves overlap until about 12 months, after which OS estimates are lower in the UK versus the US. Overall survival is very similar in the 1L immunotherapy and 1L targeted therapy groups after adjustment, while differing prior to adjustment.

Table 2. Median OS and RMST at 12 and 24 months in the UK and US by 1L drug class

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Analysis	Summary	US unweighted	US weighted	UF
	mOS (95% CI)	10.4 (9.7–11.0)	9.6 (9.0–10.2)	9.5 (8.8
Overall	12 months RMST (se)	8.0** (0.07)	7.8 (0.07)	8.2 (0
	24 months RMST (se)	12.3 (0.15)	11.9 (0.15)	12.0 (
	mOS (95% CI)	8.1 (7.5–8.7)	7.7 (7.1–8.3)	8.1 (7.4
Chemo	12 months RMST (se)	7.5 (0.09)	7.4 (0.10)	7.7 (0
	24 months RMST (se)	10.9 (0.18)	10.6 (0.19)	10.5
	mOS (95% CI)	10.2 (8.5–11.6)	13.9 (11.0–17.1)	14.0 (10
O mono.	12 months RMST (se)	7.6 (0.16)	8.31 (0.17)	8.79 (
	24 months RMST (se)	12.3 (0.34)	13.64(0.36)	14.23
	mOS (95% CI)	23.7 (22.4–27.1)	21.6 (18.5–23.7)	20.2 (16
Targeted	12 months	10.1 (0.14)	9.8 (0.15)	9.8 ((
	24 months	17.3 (0.33)	16.4 (0.35)	16.3 (
mOS=media	an overall survival. RMST	e interval. IO mono: =restricted mean su	=immunotherapy mo urvival time. se=star	onotherap ndard erro
mOS=media	an overall survival. RMST	e interval. IO mono: =restricted mean su	=immunotherapy mo urvival time. se=star	onotherap
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Extending the study period for US data to October 1, 2015 led to small reductions in OS but did not qualitatively affect study results (Supplementary Table 3). Imputing all missing ECOG PS scores as 0 or 1 did not materially change the results, while imputing as 2 or more led to higher estimates of median OS (Supplementary Table 4). For the comparison with Pilleron et al. 2023, median OS for patients receiving 1L chemotherapy was similar for the UK and US cohorts after standardisation for those aged less than 75 years (7.7 months [95% CI 7.5–7.9] for the UK versus 8.1 months [95% CI 7.8-8.5] for the US) and those 75 years or older (7.9 months [95% CI 7.5-8.2] for the UK versus 7.6 months [95% CI 7.0-8.4] for the US) (Supplementary Table 5). Probability of survival at 6 months was also similar but survival at 12 months was 5 percentage points higher for the US cohort compared to the UK cohort. TTD from the US cohort standardised to UK characteristics was 3.0 (95% CI 2.9–3.0), 4.6 (95% CI 4.0–6.0), and 9.7 (95% CI 9.0–10.9) months for patients receiving 1L chemotherapy, immunotherapy, and targeted therapy, respectively (Supplementary Table 6). In a post-hoc analysis we restricted the time period for US data to the period before the widespread adoption of immunotherapies and repeated the analyses for 1L chemotherapies only. In this analysis we saw overlapping OS curves, after standardisation, for the UK and the US (see Supplementary Figure 2). 

290 DISCUSSION

We compared OS for patients receiving 1L treatment for aNSCLC in the UK and US and found that, after adjusting for a set of common demographic and clinical characteristics, estimates of OS were similar between countries for those initiating 1L immunotherapy and targeted therapies. Estimates were similar for those initiating 1L chemotherapy for the first 12 months, after which some divergence was observed by visual inspection with OS higher in the US versus the UK. This suggests that in this population it may be reasonable to use data from the US to improve our understanding of OS for patients in the UK, where relevant local data is currently unavailable or 299 limited. This could be useful to HTA decision makers when evaluating US data. The ability to 300 make use of international data where local data is currently unavailable or limited could help 301 address decision uncertainties such as real-world outcomes, long-term survival, and time-on-302 treatment.

In addition to finding that US patients receiving 1L chemotherapy had a higher OS than UK patients after approximately 12 months, we observed a similar phenomena in the US comparison with Pilleron et al. 2023.[10] This could reflect real differences in long-term OS but could also be explained by other factors such as time-period effects, differences in censoring patterns, differences in subsequent treatment patterns, or differences in the distributions of unmeasured prognostic factors of OS across the two settings. In a post-hoc analysis, we found some indication of a time period effect with OS curves similar to when restricting US data to the period before the widespread use of immunotherapies in the US. The importance of the introduction of immunotherapies is evidenced in Snee et al. 2021, where we see higher survival over time for patients initiating therapy between 2013 and 2017 versus 2007 and 2012.[18] 

35 314

While we showed good concordance for the UK and the US in 1L treatment for aNSCLC by drug class, the generalisability of these results to other countries, indications, lines of therapy, specific products, patient subgroups, or outcomes is unclear and should be explored further. Of note, a previous study in the same indication found OS results from the US were similar to OS results from Canada (Ramagopalan et al. 2022),[8] although with greater differences identified for 1L immunotherapy than for chemotherapy.

<sup>49</sup> 50 321

A key limitation of the study relates to the UK data used for comparison. First, the study included
data from only nine sites and its representativeness to the general UK population is unknown.
However, we found similar results for 1L chemotherapy when using aggregate data reported from

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the national SACT registry.[10] Second, we did not have access to full details of the study design in the original UK retrospective study, for instance, how combination therapies consisting of more than one drug class were considered in classifying 1L and 2L therapies (except for immunotherapy which was stated to be monotherapy only). Third, we only had aggregate data for comparison. This limited our ability to further adjust for patient characteristics or subsequent lines of therapy. Fourth, the UK data had access to only a limited set of demographic and clinical characteristics and the definitions did not always align with those from the US data. There may be additional prognostic variables for which adjustment could improve comparability of OS between the UK and US (Supplementary Tables 7–9). However, it is worth noting that despite these limitations we found OS results to be comparable between the UK and the US. Currently, with the limited availability of representative and clinically-orientated local patient-level data sources, this is more likely to reflect the context in which such studies will be used to inform decision-making. Finally, it was not suitable to compare TTD, due to meaningful differences in the definitions used, which is an important outcome for health economic analyses. Future work should assess the transportability of TTD and other HTA relevant outcomes.

These results should help inform HTA reviewers when assessing the relevance of US data in the evaluation of aNSCLC therapies.

### **FIGURE LEGENDS**

Figure 1. OS curves for the UK and US before and after standardisation by 1L drug class. US data standardised to reflect average characteristics of patients in the UK for age, sex, ECOG PS score (0-1 or 2+), and histology (squamous cell, non-squamous cell, unknown). IO mono=immunotherapy monotherapy.

## 351 STATEMENTS

**Contributors** BA and PJ were responsible for the conceptualization of the study. BA, PM, SK, BB, AS, and JK were involved in the development or design of methodology. PM and BB provided support for software, formal analysis, and resourcing. BB led validation of the study results. PM and BA conducted the investigation. PM prepared visualisations of the work. SK and PJ oversaw project administration. JK and AS provided supervision of the research activities. SK and PM wrote the original draft of the manuscript. PM and BB had full access to all data in the study. All authors contributed to writing and reviewing the manuscript, and approved the submitted version.

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35 366

Declaration of interests At the time of this study, SK, PM, BB, TJR, BA, JK, and AS reported employment with Flatiron Health, Inc., which is an independent member of the Roche Group. BA conducted this work as an employee of Flatiron Health, Inc. PM, BB, TJR, BA, JK, and AS reported stock ownership in Roche. All other authors declared no competing interests. 

<sup>45</sup> 371

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to submit for publication.

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3 4	376	Data availability statement Data that support the findings of this study have been originated by
5 6	377	Flatiron Health, Inc. Requests for data sharing by licence or by permission for the specific
7 8	378	purpose of replicating results in this manuscript can be submitted to
9 10	379	publicationsdataaccess@flatiron.com.
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Evaluating transportability of overall survival estimates from US to UK populations receiving first-line treatment for advanced non-small cell lung cancer: a retrospective cohort study

### SUPPLEMENTARY MATERIALS

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## Supplementary Table 1. Pragmatic literature review

		UK publication	
Factor	Lester et al. (2021)	Snee et al. (2021)	Pilleron et al. (2023)
Peer-reviewed	Yes	Yes	No (Preprint)
Used in our analysis	Yes	No	Sensitivity analyses
Data Source	9 NHS Trusts and hospitals around the UK	Leeds Teaching hospitals	UK SACT dataset
Population of interest	Patients with stage IV advanced NSCLC	People with NSCLC	Patients with advanced NSCLC in Stages III and IV (analyses stratified by stage)
Sample Size	1003	3739	20,716
Treatment of interest	1L chemo, immunotherapy and targeted therapy	NA	Chemotherapy (Cytotoxic)
Index date anchor	1L treatment initiation	Disease diagnosis	1L treatment initiation
Study Period	2016–2019 (Enrol: 2016 to 2018)	2007–2018 (Enrol: 2007–2017)	2014–2018 (Enrol: 2014–2017)
Patient characteristics available at index	Age Sex ECOG PS Histology TNM Stage Biomarkers (high missingness)	Age Sex WHO performance status Histology TNM stage	Age Sex ECOG PS Ethnicity Treatment intent(curative vs palliative)
Death Ascertainment	Methodology not mentioned	Linkage of EMR to the Office of National Statistics death certificates	Linkage of SACT data to data from the National Cancer Registration and Analysis Service (NCRAS) data
OS Analysis	Whole cohort regardless of treatment Stratified by treatment	First stratified by disease stage(I, II, III, IV) Within each stage stratum, they stratified by tumour histology (squamous, nonsquamous,) and year of diagnosis	First stratified by disease stage (III vs IV) Within each stage stratum, they stratified by age (< 75 vs 75+)

**Search-term in pubmed**: (advanced non-small lung cancer OR aNSCLC OR advanced NSCLC OR metastatic non-small lung cancer OR met aNSCLC) AND (treatment pattern OR treatment guideline OR practice pattern OR treatment practice) AND (overall survival OR OS OR survival OR outcomes OR discontinuation OR ttd OR time on treatment OR ToT) AND (United Kingdom OR UK OR England). Filters applied: 2011 to 2022, Classical Article, Clinical Study, Comparative Study, Guideline, Meta-Analysis, Observational Study, Practice Guideline, Preprint, Review, Systematic Review. 1L=first-line. chemo=chemotherapy. ECOG PS=Eastern Cooperative Oncology Group performance status. EMR=electronic medical record. NA=not applicable.

NHS=National Health Service. NSCLC=non-small cell lung cancer. OS=overall surviva SACT=systemic anti-cancer therapy. WHO=World Health Organization.	•

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Supplementary Figure 1. Flow diagram of inclusion and exclusion criteria applied to the real-world cohort.

21 patients were excluded because their imputed death date preceded treatment start. In Flatiron Health date of death is provided at the month granularity for privacy reasons. For the analysis, the date of death is imputed to be the 15th of the month. 1L=first-line therapy. Chemo=chemotherapy. ECOG PS=Eastern Cooperative Oncology Group performance status. EHR=electronic health record. Immuno/IO=immunotherapy. Targeted=targeted therapy.

UK Any 2L Conditional on 2L Chemo	Any 287 (29%) 104 (36%)	Chemo 229 (33%)	IO 28 (16%)	Targete 30 (24%
UK Any 2L Conditional on 2L Chemo	287 (29%)	229 (33%)	28 (16%)	30 (24%
Any 2L Conditional on 2L Chemo	287 (29%)	229 (33%)	28 (16%)	30 (24%
Conditional on 2L Chemo	104 (36%)			
Chemo	104 (36%)			
		74 (32%)	26 (93%)	4(13%
IO	148 (52%)	146(64%)	2 (7%)	0 (0%)
Targeted	35 (12%)	9(4%)	0 (0%)	26 (87%
US				
Any 2L	1835 (48%)	1245 (54%)	234 (28%)	356 (53)
Conditional on 2L				
Chemo	330 (18%)	201 (16%)	105 (45%)	24 (7%
Ю	896 (49%)	827 (66%)	38 (16%)	31 (9%
Targeted	317 (17%)	65 (5%)	9 (4%)	243 (68
Other*	292 (16%)	152 (12%)	82 (35%)	58 (16%

## Supplementary Table 3. Overall survival and restricted mean survival time for the extended US cohort

$\begin{array}{c} mOS(95\%\ Cl) & 9.86\ (\\ RSMT\ at: & \\ 12\ \textit{months} & 7.9\ \\ 24\ \textit{months} & 12.\ \\ mOS(95\%\ Cl) & 7.89\ (\\ RSMT\ at: & \\ 12\ \textit{months} & 7.4\ \\ 24\ \textit{months} & 10.\ \\ 12\ \textit{months} & 7.4\ \\ 24\ \textit{months} & 10.\ \\ mOS(95\%\ Cl) & 9.63\ (\\ RSMT\ at: & \\ 12\ \textit{months} & 7.5\ \\ 24\ \textit{months} & 10.\ \\ mOS(95\%\ Cl) & 9.63\ (\\ RSMT\ at: & \\ 12\ \textit{months} & 7.5\ \\ 24\ \textit{months} & 12.\ \\ mOS(95\%\ Cl) & 9.63\ (\\ RSMT\ at: & \\ 12\ \textit{months} & 7.5\ \\ 24\ \textit{months} & 12.\ \\ mOS(95\%\ Cl) & 23.1\ (\\ RSMT\ at: & \\ 12\ \textit{months} & 9.9\ \\ 24\ \textit{months} & 16.\ \\ \\ US\ data\ standardised\ to\ reflect\ average\ characteristics\ of\ \\ score\ (O-1\ or\ 2+),\ and\ histology\ (squamous cell,\ non-squatcher)\ \\ IO\ mos\ status.\ IO=immunotherapy.\ IO\ mono=immun\ \\ survival.\ RMST=restricted\ mean\ survival\ time.\ se=standar\ \\ \end{array}$	.30–10.4)       9.23         .(0.06)       1         1(0.13)       1         .39–8.34)       7.40         .6(0.08)       1         .3(0.15)       1         .95–11.2)       13.0         .1(0.33)       1         1.0–24.9)       20.0	3 (8.71–9.79) 7.78(0.06) 1.79(0.13) 5 (7.06–8.05) 7.32(0.08) 0.55(0.16) 4 (10.9–15.7) 1 3.26(0.17) 3.50(0.35)	9.5(8.8–10.7) 8.24(0.13) 12.01(0.27) 8.1(7.4–8.9) 7.69(0.16) 10.50(0.3) 4.0(10.7–20.6) 8.79(0.31) 14.23(0.69) 20.2(16.0–30.5)
Overall (N=5106) Part (N=5106) $Part (N=5106)$ $Part (N=51$	(0.06) 1(0.13) 1 (.39-8.34) 7.40 (0.08) 1 (0.08) 1 (0.15) 1 (.95-11.2) 13.4 (0.16) 1 1(0.33) 1 1.0-24.9) 20.4	7.78(0.06) 1.79(0.13) 5 (7.06- $8.05$ ) 7.32(0.08) 0.55(0.16) 4 (10.9- $15.7$ ) 1 3.26(0.17) 3.50(0.35) 0 (17 2- $22.9$ ) 2	8.24(0.13) 12.01(0.27) 8.1(7.4–8.9) 7.69(0.16) 10.50(0.3) 4.0(10.7–20.6) 8.79(0.31) 14.23(0.69) 20 2(16 0–30 5)
$12 \text{ months} $ $12 \text$	(0.06) 1(0.13) 1 (.39-8.34) 7.40 (0.08) 7 3(0.15) 1 .95-11.2) 13.4 (0.16) 4 1(0.33) 1 1.0-24.9) 20.4	7.78(0.06) 1.79(0.13) 5 (7.06–8.05) 7.32(0.08) 0.55(0.16) 4 (10.9–15.7) 1 3.26(0.17) 3.50(0.35) 0 (17 2–22 9) 2	8.24(0.13) 12.01(0.27) 8.1(7.4–8.9) 7.69(0.16) 10.50(0.3) 4.0(10.7–20.6) 8.79(0.31) 14.23(0.69) 20.2(16.0–30.5)
24 months         12.           mOS (95% Cl)         7.89 (           RSMT at:         12 months         7.4           24 months         10.           12 months         7.4           24 months         10.           mOS (95% Cl)         9.63 (           NO mono. (N= 892)         RSMT at:           10 mono. (N= 892)         12 months           RSMT at:         12           12 months         7.5           24 months         12.           mOS (95% Cl)         23.1 (           RSMT at:         12           12 months         9.9           24 months         16.1           US data standardised to reflect average characteristics of score (0-1 or 2+), and histology (squamous cell, non-square chemo=chemotherapy. Cl=confidence interval. ECOG PS performance status. IO=immunotherapy. IO mono=immun survival. RMST=restricted mean survival time. se=standare	1(0.13)       1         .39–8.34)       7.40         .6(0.08)       -         .3(0.15)       1         .95–11.2)       13.40         .1(0.16)       -         1.0–24.9)       20.40	1.79(0.13) $5 (7.06-8.05)$ $7.32(0.08)$ $0.55(0.16)$ $4 (10.9-15.7)$ $3.26(0.17)$ $3.50(0.35)$ $0 (17 2-22 9)$	12.01(0.27) 8.1(7.4–8.9) 7.69(0.16) 10.50(0.3) 4.0(10.7–20.6) 8.79(0.31) 14.23(0.69) 20 2(16 0–30 5)
$ \begin{tabular}{l l l l l l l l l l l l l l l l l l l $	.39–8.34) 7.40 5(0.08) 7.40 3(0.15) 1 .95–11.2) 13.4 7(0.16) 4 1(0.33) 1 1.0–24.9) 20.4	5 (7.06–8.05) 7.32(0.08) 0.55(0.16) 4 (10.9–15.7) 1 3.26(0.17) 3.50(0.35)	8.1(7.4–8.9) 7.69(0.16) 10.50(0.3) 4.0(10.7–20.6) 8.79(0.31) 14.23(0.69) 20 2(16 0–30 5)
Chemo (N= 3340) RSMT at: 12 months 7.4 24 months 10. mOS (95% Cl) 9.63 ( RSMT at: 12 months 7.5 24 months 12. mOS (95% Cl) 23.1 ( RSMT at: 12 months 9.5 24 months 16.1 US data standardised to reflect average characteristics of score (0–1 or 2+), and histology (squamous cell, non-squa chemo=chemotherapy. CI=confidence interval. ECOG PS performance status. IO=immunotherapy. IO mono=immun survival. RMST=restricted mean survival time. se=standar	(0.08) 3(0.15) 1 95–11.2) 13.4 (0.16) 4 1(0.33) 1 1.0–24.9) 20.4	7.32(0.08) 0.55(0.16) 4 (10.9–15.7) 1 3.26(0.17) 3.50(0.35) 0 (17 2–22 9) 2	7.69(0.16) 10.50(0.3) 4.0(10.7–20.6) 8.79(0.31) 14.23(0.69) 20 2(16 0–30 5)
12  months = 7.4 $24  months = 10.$ $mOS (95% Cl) = 9.63 ($ $RSMT at:$ $12  months = 7.5$ $24  months = 12.$ $mOS (95% Cl) = 23.1 ($ $RSMT at:$ $12  months = 9.5$ $24  months = 9.5$ $24  months = 16.5$ US data standardised to reflect average characteristics of score (0-1 or 2+), and histology (squamous cell, non-squachemo=chemotherapy. Cl=confidence interval. ECOG PS performance status. IO=immunotherapy. IO mono=immun survival. RMST=restricted mean survival time. se=standar	(0.08)	7.32(0.08) 0.55(0.16) 4 (10.9–15.7) 1 3.26(0.17) 3.50(0.35) 0 (17 2–22 9) 2	7.69(0.16) 10.50(0.3) 4.0(10.7–20.6) 8.79(0.31) 14.23(0.69) 20 2(16 0–30 5)
24 months10.MOS (95% Cl)9.63 (NO mono. (N= 892)RSMT at:12 months7.524 months12.MOS (95% Cl)23.1 (Targeted (N= 874)RSMT at:12 months9.524 months16.1US data standardised to reflect average characteristics ofscore (0-1 or 2+), and histology (squamous cell, non-squachemo=chemotherapy. CI=confidence interval. ECOG PSperformance status. IO=immunotherapy. IO mono=immunsurvival. RMST=restricted mean survival time. se=standar	3(0.15) 1 .95–11.2) 13.4 (0.16) 3 1(0.33) 1 1.0–24.9) 20.4	0.55(0.16) 4 (10.9–15.7) 1 3.26(0.17) 3.50(0.35) 0 (17 2–22 9) 2	10.50(0.3) 4.0(10.7–20.6) 8.79(0.31) 14.23(0.69) 20 2(16 0–30 5)
MOS (95% CI) 9.63 ( RSMT at: 12 months 7.5 24 months 12. mOS (95% CI) 23.1 ( RSMT at: 12 months 9.5 24 months 9.5 24 months 16.4 US data standardised to reflect average characteristics of score (0–1 or 2+), and histology (squamous cell, non-squa chemo=chemotherapy. CI=confidence interval. ECOG PS performance status. IO=immunotherapy. IO mono=immun survival. RMST=restricted mean survival time. se=standar	.95–11.2) 13.4 (0.16) 3 1(0.33) 1 1.0–24.9) 20.4	4 (10.9–15.7) 1 3.26(0.17) 3.50(0.35)	4.0(10.7–20.6) 8.79(0.31) 14.23(0.69)
IO mono. (N= 892) IO mono. (N= 892) RSMT at: 12 months 12. mOS (95% CI) 23.1 ( RSMT at: 12 months 9.9 24 months 16.1 US data standardised to reflect average characteristics of score (0–1 or 2+), and histology (squamous cell, non-squa chemo=chemotherapy. CI=confidence interval. ECOG PS performance status. IO=immunotherapy. IO mono=immun survival. RMST=restricted mean survival time. se=standar	(0.16) (0.33) 1 1.0–24.9) 20.1	3.26(0.17) 3.50(0.35) ) (17 2–22 9) 2	8.79(0.31) 14.23(0.69) 20 2(16 0-30 5)
12 months       7.5         24 months       12.         mOS (95% CI)       23.1 (         RSMT at:       12 months         12 months       9.9         24 months       16.1         US data standardised to reflect average characteristics of score (0–1 or 2+), and histology (squamous cell, non-squa chemo=chemotherapy. CI=confidence interval. ECOG PS performance status. IO=immunotherapy. IO mono=immun survival. RMST=restricted mean survival time. se=standar	(0.16) (0.33) 1 1.0–24.9) 20.0	3.26(0.17) 3.50(0.35) 0 (17 2–22 9) 2	8.79(0.31) 14.23(0.69)
24 months12.mOS (95% Cl)23.1 (Targeted (N= 874)RSMT at:12 months9.924 months16.1US data standardised to reflect average characteristics of score (0–1 or 2+), and histology (squamous cell, non-squa chemo=chemotherapy. CI=confidence interval. ECOG PS performance status. IO=immunotherapy. IO mono=immun survival. RMST=restricted mean survival time. se=standar	1(0.33) 1 1.0–24.9) 20.0	3.50(0.35) ) (17 2–22 9) 2	14.23(0.69) 20 2(16 0–30 5)
mOS (95% Cl)       23.1 (         RSMT at:       12 months       9.9         24 months       16.1         US data standardised to reflect average characteristics of score (0–1 or 2+), and histology (squamous cell, non-squa chemo=chemotherapy. Cl=confidence interval. ECOG PS performance status. IO=immunotherapy. IO mono=immun survival. RMST=restricted mean survival time. se=standar	1.0–24.9) 20.0	) (17 2–22 9) 2	20 2(16 0-30 5)
Targeted (N= 874)       RSMT at:         12 months       9.9         24 months       16.9         US data standardised to reflect average characteristics of score (0–1 or 2+), and histology (squamous cell, non-squachemo=chemotherapy. CI=confidence interval. ECOG PS performance status. IO=immunotherapy. IO mono=immun survival. RMST=restricted mean survival time. se=standar		=	<u>.</u> (10.0-00.0)
12 months       9.5         24 months       16.         US data standardised to reflect average characteristics of score (0–1 or 2+), and histology (squamous cell, non-squa chemo=chemotherapy. CI=confidence interval. ECOG PS performance status. IO=immunotherapy. IO mono=immun survival. RMST=restricted mean survival time. se=standar			
24 months 16. US data standardised to reflect average characteristics of score (0–1 or 2+), and histology (squamous cell, non-squa chemo=chemotherapy. CI=confidence interval. ECOG PS performance status. IO=immunotherapy. IO mono=immun survival. RMST=restricted mean survival time. se=standar	(0.12)	9.67( 0.13)	9.77(0.34)
US data standardised to reflect average characteristics of score (0–1 or 2+), and histology (squamous cell, non-squa chemo=chemotherapy. CI=confidence interval. ECOG PS performance status. IO=immunotherapy. IO mono=immun survival. RMST=restricted mean survival time. se=standar	2(0.29) 1	6.08(0.30)	16.30(0.77)
	Eastern Coope otherapy monoth l error. Targeteo	rative Oncology nerapy. mOS=m d=targeted thera	Group edian overa py.
	5		

## Supplementary Table 4. Results for sensitivity analysis imputing missing ECOG PS scores

Scenario	Prevalence ECOG PS 0 or 1 after imputation (Before = 73%)	Unweighted mOS (95% CI)	Weighted mOS (95% CI)
Best (impute missing ECOG PS as 0 or 1)	78.3%	10.48 (9.89–11.04)	9.20 (8.71–9.86)
Worst (impute missing ECOG PS of 2 or more)	58.6%	10.48 (9.89–11.04)	10.32 (9.72–11.01)

CI=confidence interval. ECOG PS=Eastern Cooperative Oncology Group performance status. mOS=median overall survival.

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data mining, AI training, and similar technologies

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## Supplementary Table 5. OS results for 1L chemotherapy for US data using UK data from Pilleron et al. 2021

Analysis	Variable	US unweighted	US weighted	UK (Pilleron et al.)
	mOS (95% CI)	7.9 (7.6–8.2)	8.1 (7.8–8.5)	7.7 (7.5–7.9)
Δae < 75	Survival prob est. (%) at			
Age 10	6 months	59 (58–60)	60 (58–61)	59.7 (58.7–60.6)
	12 months	37 (36–38)	38 (36–39)	33.2 (32.3–34.1)
Age ≥ 75	mOS (95% CI)	7.1 (6.8–7.7)	7.6 (7.0–8.4)	7.9 (7.5–8.2)
	Survival prob est. (%) at			
	6 months	56 (54–59)	58 (55–61)	60.4 (58.4–62.5)
	12 months	35 (33–37)	38 (35–41)	33.4 (31.5–35.4)

US data standardised to reflect average characteristics of patients in the UK for age, sex, ECOG PS score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknown). 1L=first-line. CI=confidence interval. ECOG PS=Eastern Cooperative Oncology Group performance status. mOS=median overall survival. OS=overall survival.

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## Supplementary Table 6. Time to treatment discontinuation (TTD) from US Flatiron data before and after standardisation by 1L drug class

	Median rwTTD (95% CI)				
Analysis	Overall	Chemo	Immuno	Targeted	
US Unweighted	3.7 (3.5–3.8)	3.0 (2.9–3.0)	4.6 (4.0–6.0)	9.7 (9.0–10.9)	
US Weighted	3.4 (3.2–3.6)	3.0 (2.8–3.0)	6.2 (4.8–7.4)	9.2 (8.5–10.2)	

US data standardised to reflect average characteristics of patients in the UK for age, sex, ECOG score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknown). 1L=first-line. chemo=chemotherapy. CI=confidence interval. ECOG PS=Eastern Cooperative Oncology Group performance status. IO=immunotherapy. rwTTD=real-world time to treatment discontinuation. Targeted=targeted therapy.

10



60

Survival probability



## Supplementary Figure 2. Post-hoc analysis comparing standardised OS for patients initiating 1L chemotherapy using data from the US between 2012–2014.

US data standardised to reflect average characteristics of patients in the UK for age, sex, ECOG PS score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknown).
		Full	Model	Reduc	ed Model
Variable		Log(HR)	95% CI	Log(HR)	95% CI
Sex					
Female		••		••	••
Male		0.23	0.16–0.31	0.25	0.17–0.3
Age at treatment initiation		0.01	0.00-0.01	0.01	0.00-0.0
Race					
White		••		••	••
Non-white		-0.08	-0.18–0.01	••	••
Missing/Unknown		0.12	-0.01–0.26	••	••
Practice Type					
Community		0.	••	••	••
Academic		-0.10	-0.21–0.02	••	••
Both		-0.80	-1.20.37	••	••
Time from diagnosis to treatmen (months)	t initiation	-0.03	-0.040.01	••	••
1L initiation year					
	2016	••	••	••	••
	2017	-0.03	-0.12-0.05	••	••
	2018	-0.09	-0.22–0.04	••	••
1L Regimen Class					
Chemo		••	••		••
Immuno		-0.21	-0.310.11	-0.26	-0.350.
Targeted		-0.28	-0.480.07	-0.69	-0.800.8
ECOG PS					
0–1		••	••	••	••
2+		0.61	0.53–0.70	0.61	0.53–0.7
Tumor Pathology					
Squamous				••	
Non-squamous		-0.13	-0.230.04	-0.19	-0.270.2
Not otherwise specified		0.17	-0.01–0.36	0.14	-0.04–0.3

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	Full	Model	Reduce	d Model
Variable	Log(HR)	95% CI	Log(HR)	95% C
Smoking History				
History of smoking	••	••	••	••
No history of smoking	-0.09	-0.22-0.03	••	••
Unknown/Not documented	1.30	0.58–2.1	••	••
EGFR Status				
Mutation positive	••	••	••	••
Mutation negative	0.38	0.17–0.60	••	••
Unknown/Missing	0.49	0.26-0.73	••	••
ALK Status				
Rearrangement present		••	••	••
Rearrangement not present	0.69	0.33–1.0	••	••
Unknown/Missing	0.53	0.16–0.91	••	••
ROS1 Status				
Rearrangement present		••	••	••
Rearrangement not present	0.50	-0.04–1.0	••	••
Unknown/Missing	0.64	0.09–1.2	••	••
PD-L1 Status				
PD-L1 positive	••	••	••	••
PD-L1 negative/not detected	0.15	-0.01–0.31	••	••
Unknown/Missing	0.07	-0.07–0.20		••
Likelihood-ratio test		chi-square(df=17	)= 90.3, p<0.001	
Concordance Index	0.	647	0.6	36
1L=first-line. ALK=anaplastic lyn ECOG PS=Eastern Cooperative growth factor receptor. HR=haza death ligand 1. ROS1=ROS prof	nphoma kinase. c Oncology Group ard ratio. Immuno to-oncogene 1, re	hemo=chemothe performance sta =immunotherapy ceptor tyrosine k	erapy. CI=confi atus. EGFR=ep v. PD-L1=progr inase. Targete	dence inter idermal ammed cel d=targeted

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#### Chemo Immunotherapy Targeted 95% CI 95% CI Variable Log(HR) 95% CI Log(HR) Log(HR) Sex Female •• •• ••

Male		0.23	0.13–0.32	0.29	0.11–0.46	0.22	0.00–0.44
Age at treatment initiation		0.00	0.00-0.01	0.00	-0.01–0.01	0.02	0.01–0.04
Race							
White		••		••		••	
Non-white		-0.13	-0.250.01	-0.07	-0.29–0.15	0.13	-0.11–0.38
Missing/Unknown		0.13	-0.04-0.29	0.23	-0.07–0.52	0.03	-0.36–0.42
Practice Type							
Community				••	••	••	••
Academic		-0.02	-0.16–0.13	-0.37	-0.650.08	-0.11	-0.39–0.17
Both		-0.78	-1.3—0.28	-0.05	-1.0–0.95	-2.00	-4.00.05
Time from diagnosis to trea initiation (months)	tment	-0.04	-0.060.01	-0.02	-0.04–0.01	-0.04	-0.09–0.02
1L initiation year							
	2016	••	- (		••	••	
	2017	-0.02	-0.12-0.09	-0.19	-0.45-0.06	-0.01	-0.24-0.22
	2018	-0.03	-0.18–0.13	-0.34	-0.670.02	-0.12	-0.50-0.25
ECOG PS							
0–1		••	••			••	••
2+		0.57	0.46-0.67	0.71	0.54–0.88	0.71	0.47–0.94
Tumor Pathology							
Squamous		••	••	••	••	••	••
Non-squamous		-0.06	-0.17–0.05	-0.31	-0.520.10	-0.64	-1.20.09
NOS		0.20	-0.02–0.41	-0.11	-0.51–0.29	0.34	-0.44–1.1
Smoking History							
History of smoking		••	••	••	••	••	••
No history of smoking		-0.03	-0.21–0.14	0.04	-0.26-0.35	-0.36	-0.580.14

# Supplementary Table 8. Full model for overall survival in the US by 1L drug class

						14
	Che	emo	Immun	otherapy	Targ	eted
Variable	Log(HR)	95% CI	Log(HR)	95% CI	Log(HR)	95% CI
EGFR Status						
Mutation positive	••	••	••	••	••	••
Mutation negative	0.33	0.02–0.64	-0.86	-1.60.16	0.51	0.17–0.85
Unknown/Missing	0.40	0.05–0.74	-0.41	-1.1–0.31	0.63	0.23–1.0
ALK Status						
Rearrangement present	••	••	••	••	••	••
Rearrangement not present	0.69	-0.20–1.6	0.15	-1.0–1.3	0.65	0.19–1.1
Unknown/Missing	0.71	-0.19–1.6	-0.29	-1.5–0.94	0.68	0.17–1.2
PD-L1 Status						
PD-L1 positive	<i>.</i>	••	••	••	••	••
PD-L1 negative/not detected	0.09	-0.12-0.30	0.31	-0.10–0.72	0.27	-0.21–0.76
Unknown/Missing	-0.03	-0.22–0.17	0.05	-0.16–0.26	0.44	-0.01–0.89
				~ ~		20
Concordance Index 1L=first-line. ALK=anaplasti PS=Eastern Cooperative Or receptor. HR=hazard ratio. I Targeted=targeted therapy.	c lymphoma k ncology Grou NOS=not othe	61 kinase. chemo p performanco erwise specifio	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor GFR=epiderm programmed	nfidence inte lal growth fa cell death lig	rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplasti PS=Eastern Cooperative Or receptor. HR=hazard ratio. I Targeted=targeted therapy.	o. c lymphoma ł ncology Grou NOS=not othe	61 kinase. chemo p performanco erwise specifio	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor GFR=epiderm programmed	ofidence inte lal growth fa cell death lig	rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplasti PS=Eastern Cooperative Or receptor. HR=hazard ratio. I Targeted=targeted therapy.	o. c lymphoma ł ncology Grou NOS=not othe	61 kinase. chemo p performanco erwise specific	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor GFR=epiderm programmed	ofidence inte lal growth fa cell death lig	rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplasti PS=Eastern Cooperative Or receptor. HR=hazard ratio. I Targeted=targeted therapy.	o. c lymphoma k ncology Grou NOS=not othe	61 kinase. chemo p performanco erwise specific	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor GFR=epiderm programmed	ofidence inte lal growth fa cell death lig	rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplasti PS=Eastern Cooperative Or receptor. HR=hazard ratio. I Targeted=targeted therapy.	o. c lymphoma k ncology Grou NOS=not othe	61 kinase. chemo p performance erwise specific	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor GFR=epiderm programmed	ofidence inte lal growth fa cell death lig	rval. ECOG ctor gand 1.
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Male         0.24         0.14–0.33         0.26         0.09–0.43         0.29         0.08–           Age at treatment initiation         0.00         0.00–0.01         0.01         0.00–0.01         0.03         0.22–           ECOG PS         .	Female	••	••	••	••	••	
Age at treatment initiation         0.00         0.00-0.01         0.01         0.00-0.01         0.03         0.02- ECOG PS           0-1	Male	0.24	0.14–0.33	0.26	0.09–0.43	0.29	0.08–0.5
ECOG PS           0-1	Age at treatment initiation	0.00	0.00–0.01	0.01	0.00–0.01	0.03	0.02-0.0
0-1	ECOG PS						
2+         0.57         0.47–0.68         0.68         0.51–0.85         0.64         0.41–           Tumor Pathology           Squamous         • </td <td>0–1</td> <td></td> <td>••</td> <td>••</td> <td>••</td> <td>••</td> <td>••</td>	0–1		••	••	••	••	••
Squamous	2+	0.57	0.47–0.68	0.68	0.51–0.85	0.64	0.41–0.8
Squamous<	Tumor Pathology						
Non-squamous       -0.12       -0.22       -0.33       -0.510.14       -0.84       -1.4         NOS       0.18       -0.04-0.39       -0.15       -0.54-0.24       0.24       -0.53         Concordance Index       0.59       0.63       0.65         1L=first-line. chemo=chemotherapy. CI=confidence interval. ECOG PS=Eastern Cooperative Onco Group performance status. EGFR=epidermal growth factor receptor. HR=hazard ratio. Immuno=immunotherapy. NOS=not otherwise specified. PD-L1=programmed cell death ligand 1. Targeted=targeted therapy.	Squamous			••	••	••	••
NOS       0.18       -0.04–0.39       -0.15       -0.54–0.24       0.24       -0.53         Concordance Index       0.59       0.63       0.65         1L=first-line. chemo=chemotherapy. Cl=confidence interval. ECOG PS=Eastern Cooperative Onco Group performance status. EGFR=epidermal growth factor receptor. HR=hazard ratio. Immuno=immunotherapy. NOS=not otherwise specified. PD-L1=programmed cell death ligand 1. Targeted=targeted therapy.	Non-squamous	-0.12	-0.220.02	-0.33	-0.510.14	-0.84	-1.40.2
Concordance Index       0.59       0.63       0.65         1L=first-line. chemo=chemotherapy. Cl=confidence interval. ECOG PS=Eastern Cooperative Onco Group performance status. EGFR=epidermal growth factor receptor. HR=hazard ratio. Immuno=immunotherapy. NOS=not otherwise specified. PD-L1=programmed cell death ligand 1. Targeted=targeted therapy.	NOS	0.18	-0.04–0.39	-0.15	-0.54-0.24	0.24	-0.53–1.0
1L=first-line. chemo=chemotherapy. CI=confidence interval. ECOG PS=Eastern Cooperative Once Group performance status. EGFR=epidermal growth factor receptor. HR=hazard ratio. Immuno=immunotherapy. NOS=not otherwise specified. PD-L1=programmed cell death ligand 1. Targeted=targeted therapy.							
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# Evaluating transportability of overall survival estimates from US to UK populations receiving first-line treatment for advanced non-small cell lung cancer: a retrospective cohort study

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1	Evaluating transportability of overall survival estimates from US to UK populations
2	receiving first-line treatment for advanced non-small cell lung cancer: a retrospective
3	cohort study
4	
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#### ABSTRACT Objectives: To explore how the United Kingdom (UK) versus the United States (US) compare in patient characteristics, treatment patterns, and overall survival (OS) of patients with advanced non-small cell lung cancer (aNSCLC) initiating first-line (1L) treatment. **Design:** Retrospective cohort study. Setting: Oncology treatment centres in the US and UK. Participants: People in the US and UK diagnosed with aNSCLC and treated in the 1L setting between 2016–2018. The US cohort was obtained from a nationwide electronic health record (EHR)-derived de-identified database. The UK cohort information was derived from a published study exploring the patient characteristics, treatments, and outcomes of people with aNSCLC in the UK. Interventions: 1L chemotherapy, immunotherapy monotherapy, or targeted therapy. **Primary outcome measure:** The primary outcome was overall survival (OS)—defined as the time from treatment initiation to death from any cause. **Results:** There were 1003 patients in the UK and 3819 in the US cohorts receiving 1L therapy for aNSCLC. After standardising the US cohort to the UK cohort, median OS in the US and UK was similar across 1L drug classes: chemotherapies (7.7 [95% CI 7.1-8.3] vs. 8.1 [95% CI 7.4-8.9] months), immunotherapies (13.9 [95% CI 11.0-17.1] vs. 14.0 [95% CI 10.7-20.6]), and targeted therapies (21.6 [95% CI 18.5–23.7] vs. 20.2 [95% CI 16.0–30.5]). OS curves for 1L immunotherapy and targeted therapy were almost overlapping after standardisation. OS after around 12 months was higher in US patients compared to UK patients receiving 1L chemotherapy regimens. Of those receiving 1L chemotherapy, the proportion receiving any second-line therapy appeared higher for patients in the US vs. UK. **Conclusions:** The results suggest that in aNSCLC patients receiving 1L treatment, US data has potential to be used in technology evaluations to understand long-term OS where UK data is unavailable or sparse.

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5	51	STREM	NGTHS AND LIMITATIONS OF THIS STUDY
7 8	52	0	This study assessed the comparability of overall survival among people with aNSCLC in
9 10	53		the UK versus the US after standardising the US population to the UK population.
11 12	54	0	The study exemplifies the simple methodology that can be employed to generate empirical
13 14	55		evidence that can help HTA bodies in assessing the applicability of international evidence
15 16	56		to local decision-making.
17 18 10	57	0	Limitations include that the patient-level data were not available in the UK, as a result, we
20 21	58		used summary statistics from a recent publication in the UK, which restricted the methods
22 23	59		available for adjusting patient characteristics between the countries.
24 25	60	0	The population-adjustment was limited to patient demographic and clinical characteristics,
26 27	61		and did not include other factors that can influence transportability-eg, differences in
28 29	62		healthcare systems across countries.
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# 63 INTRODUCTION

Health technology assessment bodies require evidence on a wide and varied number of questions to inform pricing and reimbursement decisions. Common evidence types include the characteristics of the target population, natural history of disease, diagnostic and treatment patterns, use of medicines including time-on-treatment, long-term outcomes like overall survival and event rates, resource use and costs, quality of life, and the causal effects of treatment. For questions other than causal effects of treatments, real-world data is the preferred source of evidence.[1] Because the evidence must be relevant to patients treated in a given healthcare system, HTA bodies typically indicate a preference for local data.[1-3] Unfortunately, local data may not always be available or sufficient to answer all questions of interest. This is especially true where the target population is small, such as in patients expressing a rare biomarker or tumour type, where sharing of evidence across countries may be necessary to achieve sufficient statistical power.

Given that the availability of data varies across countries, it is important to understand when and how evidence from one country can be utilised to fill evidence gaps in another. Manufacturers are increasingly submitting international data to HTA bodies as part of their evidence dossiers. The most common use case beyond comparative effectiveness has been to provide data on long-term outcomes, usually overall survival but also progression-free survival and time-on-treatment, for the local standard of care to inform extrapolation and costs in economic models. Assumptions about long-term outcomes and time-on-treatment are recognised to be key drivers of cost-effectiveness but are usually subject to substantial uncertainty based on trial data alone due to limited follow-up and questions about the relevance of the trial population to the decision.[4]

Where international data has been presented, there has been variation in its acceptance across
HTA bodies but also across evaluations within HTA bodies.[5] Decision making committees are

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uncertain how to value international data given the differences between countries in terms of populations, healthcare systems and access, and clinical practice. This is expected to be a greater challenge for absolute outcomes than for comparative outcomes like relative treatment effects.[6] While informative general frameworks for considering transportability-that is, extending evidence beyond the population used in evidence generation—have been developed,[7] they are limited in their ability to guide specific decisions. For this, empirical studies on the transportability of evidence across countries is valuable; however, few such studies are currently available. One recent study found overall survival to be similar in patients receiving first-line (1L) chemotherapy or immunotherapies for advanced non-small cell lung cancer (aNSCLC) in the US and Alberta, Canada after adjusting for baseline patient demographic and clinical characteristics.[8] In this study, we aim to explore the transportability from the US to the UK of estimates of overall

survival and time-on-treatment for patients receiving different classes of drugs for 1L treatment of ich aNSCLC.

#### **METHODS**

**Data sources** 

In the absence of available individual patient-level data from the UK, we performed a pragmatic literature review to identify studies reporting outcomes for patients with aNSCLC in the UK (Supplementary Table 1). We prioritised studies that had broad population coverage, reflected current treatment practices (since the emergence of immunotherapies), and reported overall survival or time-on-treatment by treatment class. We identified three candidate studies[9-11] and selected Lester et al. 2021 for our primary analysis because it was a multicentre study reporting detailed outcomes data by 1L drug class.[9] We used Pilleron et al. 2023 for sensitivity analysis.[10] Pilleron et al. presented population level data from the national UK Systemic Anti-Cancer Treatment (SACT) registry but only for patients receiving 1L chemotherapy regimens. We 

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excluded Snee et al. 2021 because the study did not describe the patient characteristics of
patients with advanced disease and outcomes were reported from diagnosis rather than initiation
of treatment.[11]

Data for patients treated in the United States came from the nationwide electronic health record (EHR)-derived, de-identified Flatiron Health database—a longitudinal database comprising structured and unstructured data curated using technology enabled human abstraction.[12] At the time of this study, de-identified patient-level data were derived from ~280 US cancer clinics (~800 sites of care) and rule-based lines of therapy were defined by expert oncology clinicians. The data processing and quality assurance procedures for Flatiron Health data are described in detail elsewhere.[13]

<sup>2</sup> 126

# 127 Study population

The UK patient population was based on a retrospective real-world study that identified patients from nine UK centres who initiated 1L systemic anticancer therapy between June 1, 2016, and March 31, 2018 and had a median follow-up of 9.2 months.[9] Patients were included if they were 18 years of age or older, were diagnosed with metastatic disease, were not enrolled in a clinical trial during the study period, and were not missing relevant data (date of diagnosis, age, sex, Eastern Cooperative Oncology Group [ECOG] performance status [PS], histology, and response). We applied comparable inclusion criteria to the US data to match the population included in the UK study. We restricted analysis to patients with a lung cancer diagnosis (ICD-9 162.x or ICD-10 C34x or C39.9); at least two documented clinical visits; pathology consistent with aNSCLC that was confirmed using unstructured data; stage IV disease (confirmed using unstructured data); aged 18 years or older at diagnosis; treatment naive; were exposed to relevant therapies in 1L; were not enrolled in clinical trials during the study period; had no gaps between diagnosis and EHR activity exceeding 90 days to ensure more complete treatment information, and had ECOG

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PS recorded within 30 days of the index date. The UK EHR study did not report how they categorised combination therapies comprising more than one drug class, although such combinations are expected to be rare. We excluded patients with such combination therapies from the US cohort when categorising 1L treatment. Patients were selected for the US cohort over the same time period as the UK study. The Institutional Review Board of WCG IRB (Reference #: IRB00000533) gave ethical approval for the study protocol prior to study conduct and included a waiver of informed consent.

# 149 Outcomes

The study outcomes of interest were overall survival (OS) and time-to-treatment discontinuation (TTD). Overall survival was defined in both cohorts as time from initiation of 1L treatment to the date of death from any cause. Both studies have reported high sensitivity and specificity for mortality.[14.15] For the US cohort, TTD was defined as time from initiation of 1L therapy to the last drug episode for the specific drug of interest in the 1L, which is consistent with standard definitions in HTA. For the UK cohort, TTD was defined as time from initiation of 1L therapy to the start of the last cycle of therapy (which will tend to underestimate true TTD). Since TTD was defined differently between these studies, we present US TTD outcomes for completeness but do not compare them with UK TTD. UK patients were censored at the earliest of the end of the study period or the date of last assessment; US patients were censored at the earliest of the end of the study period or at the last activity recorded in the EHR.

# 162 Analysis

We compared baseline characteristics for all variables available for the UK cohort plus additional
 variables for the US cohort, noting differences in definitions where present, for all 1L aNSCLC
 treatment and by drug class (chemotherapy, immunotherapy, or targeted therapies). We also
 presented differences in use of second-line (2L) therapies after 1L. Comparison of 2L therapies

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is limited by uncertainty as to how combination therapies consisting more than one drug class were categorised in the UK cohort study.

We used the matching-adjustment indirect comparison (MAIC) approach to standardise the characteristics of US patients to those of UK patients represented in Lester et al. 2021. We selected MAIC because it enabled us to standardise individual patient data from the US using summary/published data from the UK. MAIC estimated weights to ensure that the average characteristics of the US study population matched those of the UK study population. Specifically, we standardised the US study population to match the average characteristics (age, sex, ECOG PS score [0–1 or 2+], and histology [squamous cell, non-squamous cell, unknown]) of patients in the UK, overall and by 1L drug class.[16] We compared OS between UK and US patients before and after standardisation, and Kaplan-Meier survival curves (KM), median survival, and restricted mean survival time (RMST) at 12 and 24 months from the index date of 1L treatment initiation. Published KM figures from the UK study were digitised and reproduced here following the algorithm from Guyot et al. 2012.[17] Our comparison is purely descriptive—we do not perform hypothesis tests of transportability because there is no established threshold for when results can be considered transportable; this will depend on the use case and decision context including the amount of decision uncertainty. To explore whether we were unable to account for important prognostic variables in our standardisation model, we modelled OS in the US cohort using Cox proportional hazards model regression conditional on 1L drug class (for the overall model only), age, sex, ECOG PS score, histology, race, year, time since diagnosis to treatment initiation, smoking history, and biomarker status (ALK, ROS1, EGFR, PD-L1) and compared models using likelihood ratio tests using 5% significance level.

We performed several sensitivity analyses. First, we extended the enrolment window for US data to October 1, 2015 to reflect when immunotherapies first became available for aNSCLC in the US

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and repeated the primary analysis. Second, rather than excluding people with missing ECOG PS scores in the US data, we imputed ECOG PS assuming best (ECOG PS 0 or 1) and worst (ECOG PS 2+) and repeated the primary analysis. Third, we repeated the main analysis using data from Pilleron et al. (2023) for comparison. The study by Pilleron et al. included adult patients with aNSCLC treated with chemotherapy between 2014 to 2017 in the UK followed until the end of 2018 and presented results by disease stage (III, IV) and age (<= 75, >75 years). We selected US patients from the same time period and standardised the US study population to match the average characteristics of patients in stage IV in terms of age, sex, race (white, non-white), and baseline ECOG PS score. Additional details for the study by Pilleron et al. can be found in Supplementary table 1. 

Finally, we undertook a post-hoc analysis to explore the potential role of time-period effects on observed differences in outcomes for patients treated with 1L chemotherapy, hypothesising that the earlier and faster uptake of immunotherapies in the US may impact comparability. To explore this, we compared OS for patients in the UK with patients in the US receiving 1L chemotherapy regimens before the widespread availability of immunotherapies, i.e., those initiating 1L treatment between June 1, 2012, and March 31, 2014.

- 211 Patient and public involvement
- 212 None.

<sup>45</sup> 213

<sup>47</sup> 48 214 **RESULTS** 

The UK cohort included 1003 patients meeting the inclusion criteria, with 69.6%, 17.8%, and
12.6% of patients initiating chemotherapy, immunotherapy, and targeted therapy, respectively.
After applying inclusion criteria, the US cohort included 3819 patients initiating 1L therapy

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(Supplementary Figure 1). Of these patients, 60.6%, 21.9%, and 17.5% initiated chemotherapy,
immunotherapy, and targeted therapy, respectively (Table 1 and Supplementary Table 2).

Age and sex distributions were similar in the US and UK populations regardless of 1L therapy (Table 1). The median age was 68 years (range 28–93) for UK patients and 69 years (IQR 61– 76; range 21–81) for US patients. 541 (53.9%) patients in the UK were male compared to 2013 (52.7%) in the US. Most patients in the two cohorts had ECOG PS scores of 0 or 1 (759 [75.7%] in the UK versus 2786 [73.0%] in the US). The proportion of patients with ECOG PS scores of 0 or 1 were higher in the UK compared to the US for patients initiating immunotherapies and lower for those initiating targeted therapies. The mix of lung cancer histology types differed slightly between the countries, with the proportion of patients with non-squamous cell disease being lower in the UK compared to the US cohort (641 [63.9%] versus 2684 [70.3%]), but missing data on histology was greater in the UK. Biomarker prevalence rates were not comparable due to different classifications used. Median follow-up was 9.0 months in the US versus 9.2 months in the UK but this varied substantially by 1L drug class.

A lower proportion of patients went on to receive 2L treatment in the UK compared to the US: 287 (29%) patients in the UK versus 1835 (48%) in the US (Supplementary Table 3), though this may partly be driven by differences in censoring rates and how the 2L combination therapies were classified. Excluding 2L combination therapies consisting of more than one drug class for patients in the US leads to a switching rate of 40%. This pattern is observed regardless of 1L drug class.

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	. 1

Table 1. Dasenne charact	teristics and	d details of	follow-up fo	r patients i	n the UK an	d US by 1L dru	ign class	
	Ove	erall	1L Ch	emo	1L IO m	onotherapy	ng 7 L targ	eted thei
Characteristic	UK (n=1003)	US (n=3819)	UK (n= 698)	US (n=2313)	UK (n = 179)	US (n=836)	for U∰K (n = ເຮ m ຊີ126)	US (n
Proportion of study pop., %	100	100	69.6	60.6	17.8	21.9	nber 2 nseigr s rela	17
Median follow-up (range*), months	9.2 (0.0– 42.7)	9.0 (0.0– 42.9)	7.9 (0.0– 42.7)	7.3 (0.0– 42.9)	12.7 (0.1– 37.3)	8.1 (0.0–42.3)	023 (0.1- to 27.1)	20.3 (0.
Median age(range*), years	68 (28–93)	69 (21–81)	68 (28–88)	69 (21–81)	67 (48–90)	71(38–81)		69 (2
Sex, n (%)				1311			oaded fi erieur ( and dat	
Male	541 (53.9)	2013 (52.7)	395 (56.6)	(56.7)	94 (52.5)	439 (52.5)	a mir (41.3)	263 (
Female	462 (46.1)	1806 (47.3)	303 (43.4)	1002 (43.3)	85 (47.5)	397 (47.5)	ning, · 79 (58.7)	407 (
Tumour histology, n (%)							/bmjc Al tra	
Squamous	243 (24.2)	957 (25.1)	202 (28.9)	730 (31.6)	38 (21.2)	210 (25.1)	aining (2.4)	17 (
Non-squamous	641(63.9)	2684 (70.3)	391 (56.0)	1460 (63.1)	133(74.3)	584 (69.9)	and 177 (92.9)	640 (
Not specified	119 (11.9)	178 (4.7)	105 (15.0)	123 (5.3)	8 (4.5)	42 (5.0)	simi (4.8)	13 (
ECOG PS score, n (%)							on Ju lar te	
0–1	759 (75.7)	2786 (73.0)	513 (73.5)	1714 (74.1)	157 (87.7)	556 (66.5)	chnol 89 (70.6)	516 (
2+	244 (24.3)	1033 (27.0)	185 (26.5)	599 (25.9)	22 (12.3)	280 (33.5)	200 (29.4)	154 (
EGFR Status, No. (%)							5 at /	
Mutation positive	108 (10.8)	556 (14.6)	1 (0.1)	65 (2.8)	0 (0.0)	11 (1.3)	1 <b>0</b> 7 (84.9)	480 (
Mutation negative	••	2078 (54.4)		1333 (57.6)		613 (73.3)	e Bit	132 (
		1185 (31.0)		015 (30 6)		212(254)	olio	59 (

							en-2024- copyrigh		
	Ove	erall	1L Ch	emo	1L IO m	onotherapy	0857: 1t, inc	L targe	ted ther
Characteristic	UK (n=1003)	US (n=3819)	UK (n= 698)	US (n=2313)	UK (n = 179)	US (n=836)	20017	(n = 6)	US (n:
ALK Status, No. (%)							Dec		
Rearrangement present	19 (1.9)	97 (2.5)	0 (0.0)	8 (0.3) 1302	0 (0.0)	5 (0.6)	ernber Enseig Ises rel	5.1)	84 (1
Rearrangement not present	••	2332 (61.1)	••	(56.3) 1003	••	604 (72.2)	2024. [ Inemer lated to	•	426 (6
Unknown/Missing	••	1390 (36.4)	••	(43.4)	••	227 (27.2)	nt Su	•	160 (2
<i>PDL1</i> Status**, No. (%)							nloac Iperio It and		
PD-L1 positive	182 (18.1)	1486 (38.9)	3 (0.4)	586 (25.3)	179 (100)	669 (80.0)	dateur (C	).0)	231 (3
PD-L1 negative/not detected	••	728 (19.1)	64	535 (23.1)	••	39 (4.7)	rom http ABES) a mining	•	154 (2
Unknown/Missing	••	1605 (42.0)		(51.5)	••	128 (15.3)	g, Al	•	285 (4
*Lester et al.,(2021) only r	eported rang	ge. ALK=ana	aplastic lymph	noma kinase	e. chemo=ch	emotherapy. EC	∰g <mark>e</mark> jes	=Easte	ərn
Cooperative Oncology Gro	oup perform	ance status.	EGFR=epide	ermal growtl	n factor recep	otor. IO=immund	≣ Setheteap	y. PDL	1/PD-
L1=programmed cell death	n ligand 1. *	*In the US a	nalysis, patiei	nts were co	nsidered PD-	L1 positive if the	ang Berland Be	1 tumo	ur propo
score was ≥ 1% or if there	was referer	nce to PD-L1	I positivity in t	the medical	chart. This ta	able presents va	a <u>e</u> iabjes	that w	ere com
between the US and UK a Table 2.	nalyses. Ad	ditional varia	ables that wer	e measured	d in the US st	tudy only can be	artouune .	in Sup	plement
							11, 2025 a ologies.		
							at Agen		
							ice Bib		
							liogra		
							bhi		

Conditional on receiving 2L therapy, the proportion of people receiving immunotherapies was comparable (52% in UK versus 49% in US) but patients in the UK were more likely to receive other chemotherapy regimens (36% in UK versus 18% in US) and less likely to receive targeted therapy (12% in UK versus 16% in US). As shown in Supplementary Table 3, conditional on the 1L therapy received, there were large differences in the proportion of UK versus US patients who went on to receive 2L therapies.

The median OS across all therapies was 9.5 months (95% confidence interval [CI] 8.8-10.7) in the UK compared to 10.4 months (95% CI 9.7–11.0) in the US prior to population adjustment (standardisation) (Table 2). After population adjustment, median OS in the US (9.6 months [9.0-10.2]) was more similar to median OS in the UK, indicating the importance of matching patient characteristics across both countries. Adjusted median OS was similar in the UK and US for 1L chemotherapy (8.1 months [95% CI 7.4–8.9] in the UK versus 7.7 months [95% CI 7.1–8.3] in the US), immunotherapy (14.0 months [95% CI 10.7-20.6] in the UK versus 13.9 months [95% CI 11.0-17.1] in the US), and targeted therapy (20.2 months [95% CI 16.0-30.5] in the UK versus 21.6 months [95% CI 18.5–23.7] in the US). Similar patterns were observed for RMST at 12 and 24 months.

OS curves exhibited a similar shape for each 1L drug class over the duration of follow-up (Figure 1). In general, the OS curves were similar and overlapping in all treatment groups once the data was adjusted to match patient characteristics. For 1L chemotherapy—irrespective of adjustment (standardisation)—the OS curves overlap until about 12 months, after which OS estimates are lower in the UK versus the US. Overall survival is very similar in the 1L immunotherapy and 1L targeted therapy groups after adjustment, while differing prior to adjustment.

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mOS (95% Cl)         10.4 (9.7–11.0)         9.6 (9.0–10.2)         9.5 (8.8           Overall         12 months RMST (se)         8.0" (0.07)         7.8 (0.07)         8.2 (0.24           24 months RMST (se)         12.3 (0.15)         11.9 (0.15)         12.0 (0.07)           mOS (95% Cl)         8.1 (7.5–8.7)         7.7 (7.1–8.3)         8.1 (7.4           Chemo         12 months RMST (se)         7.5 (0.09)         7.4 (0.10)         7.7 (0.10)           24 months RMST (se)         10.9 (0.18)         10.6 (0.19)         10.5 (0.10)           24 months RMST (se)         10.9 (0.18)         10.6 (0.19)         10.5 (0.10)           mOS (95% Cl)         10.2 (8.5–11.6)         13.9 (11.0–17.1)         14.0 (10.0)           IO mono.         12 months RMST (se)         7.6 (0.16)         8.31 (0.17)         8.79 (0.10)           24 months RMST (se)         12.3 (0.34)         13.64(0.36)         14.23           mOS (95% Cl)         23.7 (22.4–27.1)         21.6 (18.5–23.7)         20.2 (16.1)           12 months RMST (se)         10.1 (0.14)         9.8 (0.15)         9.8 (0.21)           24 months RMST (se)         17.3 (0.33)         16.4 (0.35)         16.3 (0.3)           US data standardised to reflect average characteristics of patients in the UK for age, s         ECOG	Analysis	Summary	US unweighted	US weighted	UK
Overall         12 months RMST (se)         8.0" (0.07)         7.8 (0.07)         8.2 (0.17)           24 months RMST (se)         12.3 (0.15)         11.9 (0.15)         12.0 (0.15)           mOS (95% Cl)         8.1 (7.5–8.7)         7.7 (7.1–8.3)         8.1 (7.5–8.7)           Chemo         12 months RMST (se)         7.5 (0.09)         7.4 (0.10)         7.7 (0.10)           24 months RMST (se)         10.9 (0.18)         10.6 (0.19)         10.5           MOS (95% Cl)         10.2 (8.5–11.6)         13.9 (11.0–17.1)         14.0 (10.10)           10 mono.         12 months RMST (se)         7.6 (0.16)         8.31 (0.17)         8.79 (0.10)           24 months RMST (se)         12.3 (0.34)         13.64(0.36)         14.23 (0.15)         9.8 (0.15)         9.8 (0.15)           12 months RMST (se)         10.1 (0.14)         9.8 (0.15)         9.8 (0.15)         9.8 (0.15)         9.8 (0.15)         9.8 (0.15)         9.8 (0.15)         9.8 (0.15)         9.8 (0.15)         9.8 (0.16)         9.8 (0.16)         9.8 (0.16)         9.8 (0.16)         9.8 (0.16)         9.8 (0.16)         9.8 (0.16)         9.8 (0.16)         9.8 (0.16)         9.8 (0.16)         9.8 (0.16)         9.8 (0.16)         9.8 (0.16)         9.8 (0.16)         9.8 (0.16)         9.8 (0.16)         9.8 (0.16)		mOS (95% CI)	10.4 (9.7–11.0)	9.6 (9.0–10.2)	9.5 (8.8–
24 months RMST (se)         12.3 (0.15)         11.9 (0.15)         12.0 (           mOS (95% Cl)         8.1 (7.5–8.7)         7.7 (7.1–8.3)         8.1 (7.4           Chemo         12 months RMST (se)         7.5 (0.09)         7.4 (0.10)         7.7 (7.1–8.3)           24 months RMST (se)         10.9 (0.18)         10.6 (0.19)         10.5           24 months RMST (se)         10.2 (8.5–11.6)         13.9 (11.0–17.1)         14.0 (10.10)           IO mono.         12 months RMST (se)         7.6 (0.16)         8.31 (0.17)         8.79 (1.23)           24 months RMST (se)         12.3 (0.34)         13.64(0.36)         14.23           mOS (95% Cl)         23.7 (22.4–27.1)         21.6 (18.5–23.7)         20.2 (16.10)           Targeted         12 months RMST (se)         10.1 (0.14)         9.8 (0.15)         9.8 (0.15)           24 months RMST (se)         17.3 (0.33)         16.4 (0.35)         16.3 (1.20)           US data standardised to reflect average characteristics of patients in the UK for age, s         ECOG PS score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknow chemo=chemotherapy. Cl=confidence interval. IO mono=immunotherapy monotherapy monotherapy mos=median overall survival. RMST=restricted mean survival time. se=standard error	Overall	12 months RMST (se)	8.0** (0.07)	7.8 (0.07)	8.2 (0.1
mOS (95% Cl)         8.1 (7.5–8.7)         7.7 (7.1–8.3)         8.1 (7.4           Chemo         12 months RMST (se)         7.5 (0.09)         7.4 (0.10)         7.7 (0.10)           24 months RMST (se)         10.9 (0.18)         10.6 (0.19)         10.5           MOS (95% Cl)         10.2 (8.5–11.6)         13.9 (11.0–17.1)         14.0 (10.10)           IO mono.         12 months RMST (se)         7.6 (0.16)         8.31 (0.17)         8.79 (1.24)           IO mono.         12 months RMST (se)         12.3 (0.34)         13.64(0.36)         14.23           IOS (95% Cl)         23.7 (22.4–27.1)         21.6 (18.5–23.7)         20.2 (16.123)           Targeted         12 months RMST (se)         10.1 (0.14)         9.8 (0.15)         9.8 (0.15)           US data standardised to reflect average characteristics of patients in the UK for age, st ECOG PS score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknow chemo=chemotherapy. Cl=confidence interval. IO mono=immunotherapy montherapy mosterapy mOS=median overall survival. RMST=restricted mean survival time. se=standard error		24 months RMST (se)	12.3 (0.15)	11.9 (0.15)	12.0 (0.
Chemo         12 months RMST (se)         7.5 (0.09)         7.4 (0.10)         7.7 (0.24 months RMST (se)           24 months RMST (se)         10.9 (0.18)         10.6 (0.19)         10.5           mOS (95% Cl)         10.2 (8.5–11.6)         13.9 (11.0–17.1)         14.0 (10.0)           10 mono.         12 months RMST (se)         7.6 (0.16)         8.31 (0.17)         8.79 (0.20)           24 months RMST (se)         12.3 (0.34)         13.64(0.36)         14.23 (0.20)           mOS (95% Cl)         23.7 (22.4–27.1)         21.6 (18.5–23.7)         20.2 (16.0)           Targeted         12 months RMST (se)         10.1 (0.14)         9.8 (0.15)         9.8 (0.0)           24 months RMST (se)         17.3 (0.33)         16.4 (0.35)         16.3 (0.20)         16.3 (0.20)           US data standardised to reflect average characteristics of patients in the UK for age, s         ECOG PS score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknow chemo=chemotherapy. Cl=confidence interval. IO mono=immunotherapy monotherapy mosterapy mos=median overall survival. RMST=restricted mean survival time. se=standard error		mOS (95% CI)	8.1 (7.5–8.7)	7.7 (7.1–8.3)	8.1 (7.4-
24 months RMST (se)         10.9 (0.18)         10.6 (0.19)         10.5           mOS (95% Cl)         10.2 (8.5–11.6)         13.9 (11.0–17.1)         14.0 (10.0)           10 mono.         12 months RMST (se)         7.6 (0.16)         8.31 (0.17)         8.79 (10.0)           24 months RMST (se)         12.3 (0.34)         13.64(0.36)         14.23           mOS (95% Cl)         23.7 (22.4–27.1)         21.6 (18.5–23.7)         20.2 (16.0)           Targeted         12 months RMST (se)         10.1 (0.14)         9.8 (0.15)         9.8 (0.20)           24 months RMST (se)         17.3 (0.33)         16.4 (0.35)         16.3 (10.0)           US data standardised to reflect average characteristics of patients in the UK for age, s         ECOG PS score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknot chemo=chemotherapy. Cl=confidence interval. IO mono=immunotherapy mootherapy moS=median overall survival. RMST=restricted mean survival time. se=standard error	Chemo	12 months RMST (se)	7.5 (0.09)	7.4 (0.10)	7.7 (0.
IO mono.         10.2 (8.5–11.6)         13.9 (11.0–17.1)         14.0 (10.10)           12 months RMST (se)         7.6 (0.16)         8.31 (0.17)         8.79 (10.12)           24 months RMST (se)         12.3 (0.34)         13.64(0.36)         14.23           mOS (95% Cl)         23.7 (22.4–27.1)         21.6 (18.5–23.7)         20.2 (16.10)           Targeted         12 months RMST (se)         10.1 (0.14)         9.8 (0.15)         9.8 (0.10)           24 months RMST (se)         17.3 (0.33)         16.4 (0.35)         16.3 (10.17)           US data standardised to reflect average characteristics of patients in the UK for age, s         ECOG PS score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknow chemo=chemotherapy. Cl=confidence interval. IO mono=immunotherapy monotherapy monotherapy           mOS=median overall survival. RMST=restricted mean survival time. se=standard error		24 months RMST (se)	10.9 (0.18)	10.6 (0.19)	10.5 (0
IO mono.         12 months RMST (se)         7.6 (0.16)         8.31 (0.17)         8.79 (           24 months RMST (se)         12.3 (0.34)         13.64(0.36)         14.23           mOS (95% Cl)         23.7 (22.4–27.1)         21.6 (18.5–23.7)         20.2 (16.           Targeted         12 months RMST (se)         10.1 (0.14)         9.8 (0.15)         9.8 (0.2000)           24 months RMST (se)         17.3 (0.33)         16.4 (0.35)         16.3 (0.2000)           US data standardised to reflect average characteristics of patients in the UK for age, s         ECOG PS score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknow chemo=chemotherapy. Cl=confidence interval. IO mono=immunotherapy monotherapy most and error           mOS=median overall survival. RMST=restricted mean survival time. se=standard error		mOS (95% CI)	10.2 (8.5–11.6)	13.9 (11.0–17.1)	14.0 (10.7
24 months RMST (se)12.3 (0.34)13.64(0.36)14.23mOS (95% Cl)23.7 (22.4–27.1)21.6 (18.5–23.7)20.2 (16.12 months RMST (se)10.1 (0.14)9.8 (0.15)9.8 (0.20)24 months RMST (se)17.3 (0.33)16.4 (0.35)16.3 (0.33)US data standardised to reflect average characteristics of patients in the UK for age, sECOG PS score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknow chemo=chemotherapy. Cl=confidence interval. IO mono=immunotherapy monotherapymOS=median overall survival. RMST=restricted mean survival time. se=standard error	IO mono.	12 months RMST (se)	7.6 (0.16)	8.31 (0.17)	8.79 (0.
mOS (95% Cl)23.7 (22.4–27.1)21.6 (18.5–23.7)20.2 (16.7)12 months RMST (se)10.1 (0.14)9.8 (0.15)9.8 (0.15)24 months RMST (se)17.3 (0.33)16.4 (0.35)16.3 (10.10)US data standardised to reflect average characteristics of patients in the UK for age, sECOG PS score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknowchemo=chemotherapy. Cl=confidence interval. IO mono=immunotherapy monotherapymOS=median overall survival. RMST=restricted mean survival time. se=standard error		24 months RMST (se)	12.3 (0.34)	13.64(0.36)	14.23 (0
Targeted       12 months RMST (se)       10.1 (0.14)       9.8 (0.15)       9.8 (0.15)         24 months RMST (se)       17.3 (0.33)       16.4 (0.35)       16.3 (0.15)         US data standardised to reflect average characteristics of patients in the UK for age, s       ECOG PS score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknow chemo=chemotherapy. CI=confidence interval. IO mono=immunotherapy monotherapy         mOS=median overall survival. RMST=restricted mean survival time. se=standard error		mOS (95% CI)	23.7 (22.4–27.1)	21.6 (18.5–23.7)	20.2 (16.0
24 months RMST (se) 17.3 (0.33) 16.4 (0.35) 16.3 ( US data standardised to reflect average characteristics of patients in the UK for age, s ECOG PS score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknow chemo=chemotherapy. CI=confidence interval. IO mono=immunotherapy monotherapy mOS=median overall survival. RMST=restricted mean survival time. se=standard error	Targeted	12 months RMST (se)	10 1 (0 14)	9.8 (0.15)	0 8 <i>(</i> 0 <i>'</i>
US data standardised to reflect average characteristics of patients in the UK for age, s ECOG PS score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unkno chemo=chemotherapy. CI=confidence interval. IO mono=immunotherapy monotherapy mOS=median overall survival. RMST=restricted mean survival time. se=standard error	laigotoa			( )	3.0 (0.
	US data sta ECOG PS s chemo=che mOS=medi	24 months RMST (se) andardised to reflect avera score (0–1 or 2+), and his emotherapy. CI=confidenc an overall survival. RMST	17.3 (0.33) age characteristics of tology (squamous c e interval. IO mono- r=restricted mean su	16.4 (0.35) If patients in the UK ell, non-squamous of immunotherapy mo irvival time. se=star	16.3 (0 for age, se cell, unknov onotherapy idard error.
	US data sta ECOG PS s chemo=che mOS=medi	24 months RMST (se) andardised to reflect avera score (0–1 or 2+), and his emotherapy. CI=confidenc an overall survival. RMST	17.3 (0.33) age characteristics of tology (squamous c e interval. IO mono- r=restricted mean su	16.4 (0.35) If patients in the UK ell, non-squamous of immunotherapy mo irvival time. se=star	16.3 (0 for age, se cell, unknov onotherapy idard error.
	US data sta ECOG PS s chemo=che mOS=medi	24 months RMST (se) andardised to reflect avera score (0–1 or 2+), and his emotherapy. CI=confidenc an overall survival. RMST	17.3 (0.33) age characteristics of tology (squamous c e interval. IO mono- =restricted mean su	16.4 (0.35) If patients in the UK ell, non-squamous of immunotherapy mo irvival time. se=star	16.3 (0. for age, se cell, unknow onotherapy. ndard error.
	US data sta ECOG PS s chemo=che mOS=medi	24 months RMST (se) andardised to reflect avera score (0–1 or 2+), and his emotherapy. CI=confidenc an overall survival. RMST	17.3 (0.33) age characteristics of tology (squamous c e interval. IO mono- =restricted mean su	16.4 (0.35) If patients in the UK ell, non-squamous of immunotherapy mo irvival time. se=star	16.3 (0. for age, se cell, unknow onotherapy. ndard error.
	US data sta ECOG PS s chemo=che mOS=medi	24 months RMST (se) andardised to reflect avera score (0–1 or 2+), and his emotherapy. CI=confidenc ian overall survival. RMST	17.3 (0.33) age characteristics of tology (squamous c e interval. IO mono =restricted mean su	16.4 (0.35) If patients in the UK ell, non-squamous of immunotherapy mo irvival time. se=star	16.3 (0 for age, se cell, unknov onotherapy ndard error.
	US data sta ECOG PS s chemo=che mOS=medi	24 months RMST (se) andardised to reflect avera score (0–1 or 2+), and his emotherapy. CI=confidenc an overall survival. RMST	17.3 (0.33) age characteristics of tology (squamous c e interval. IO mono- =restricted mean su	16.4 (0.35) If patients in the UK ell, non-squamous of immunotherapy mo irvival time. se=star	16.3 (0 for age, se cell, unknov onotherapy ndard error.
	US data sta ECOG PS s chemo=che mOS=medi	24 months RMST (se) andardised to reflect avera score (0–1 or 2+), and his emotherapy. CI=confidenc an overall survival. RMST	17.3 (0.33) age characteristics of tology (squamous c e interval. IO mono- =restricted mean su	16.4 (0.35) If patients in the UK ell, non-squamous of immunotherapy mo irvival time. se=star	16.3 (0 for age, se cell, unknov onotherapy indard error.
	US data sta ECOG PS s chemo=che mOS=medi	24 months RMST (se) andardised to reflect avera score (0–1 or 2+), and his emotherapy. CI=confidenc an overall survival. RMST	17.3 (0.33) age characteristics of tology (squamous c e interval. IO monos =restricted mean su	16.4 (0.35) If patients in the UK ell, non-squamous of immunotherapy mo irvival time. se=star	16.3 (0 for age, se cell, unknov onotherapy idard error.
	US data sta ECOG PS s chemo=che mOS=medi	24 months RMST (se) andardised to reflect avera score (0–1 or 2+), and his emotherapy. CI=confidence ian overall survival. RMST	17.3 (0.33) age characteristics of tology (squamous che interval. IO mono "=restricted mean su	16.4 (0.35) If patients in the UK ell, non-squamous of immunotherapy mo irvival time. se=star	16.3 (0. for age, se cell, unknov onotherapy. ndard error.
	US data sta ECOG PS s chemo=che mOS=medi	24 months RMST (se) andardised to reflect avera score (0–1 or 2+), and his emotherapy. CI=confidence ian overall survival. RMST	17.3 (0.33) age characteristics of tology (squamous che interval. IO monos =restricted mean su	16.4 (0.35) If patients in the UK ell, non-squamous of immunotherapy mo irvival time. se=star	16.3 (0 for age, se cell, unknov onotherapy. ndard error.

Extending the study period for US data to October 1, 2015, led to small reductions in OS but did not qualitatively affect study results (Supplementary Table 4). Imputing all missing ECOG PS scores as 0 or 1 did not materially change the results, while imputing as 2 or more led to higher estimates of median OS (Supplementary Table 5). For the comparison with Pilleron et al. 2023, median OS for patients receiving 1L chemotherapy was similar for the UK and US cohorts after standardisation for those aged less than 75 years (7.7 months [95% CI 7.5–7.9] for the UK versus 8.1 months [95% CI 7.8-8.5] for the US) and those 75 years or older (7.9 months [95% CI 7.5-8.2] for the UK versus 7.6 months [95% CI 7.0-8.4] for the US) (Supplementary Table 6). Probability of survival at 6 months was also similar but survival at 12 months was 5 percentage points higher for the US cohort compared to the UK cohort. TTD from the US cohort standardised to UK characteristics was 3.0 (95% CI 2.9–3.0), 4.6 (95% CI 4.0–6.0), and 9.7 (95% CI 9.0–10.9) months for patients receiving 1L chemotherapy, immunotherapy, and targeted therapy, respectively (Supplementary Table 7). In a post-hoc analysis we restricted the time period for US data to the period before the widespread adoption of immunotherapies and repeated the analyses for 1L chemotherapies only. In this analysis we saw overlapping OS curves, after standardisation, for the UK and the US (see Supplementary Figure 2). DISCUSSION We compared OS for patients receiving 1L treatment for aNSCLC in the UK and US and found that, after adjusting for a set of common demographic and clinical characteristics, estimates of OS were similar between countries for those initiating 1L immunotherapy and targeted therapies. Estimates were similar for those initiating 1L chemotherapy for the first 12 months, after which

some divergence was observed by visual inspection with OS higher in the US versus the UK. This suggests that in this population it may be reasonable to use data from the US to improve our understanding of OS for patients in the UK, where relevant local data is currently unavailable or limited. This could be useful to HTA decision makers when evaluating US data. The ability to

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make use of international data where local data is currently unavailable or limited could help
address decision uncertainties such as real-world outcomes, long-term survival, and time-ontreatment.

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In addition to finding that US patients receiving 1L chemotherapy had a higher OS than UK patients after approximately 12 months, we observed a similar phenomenon in the US comparison with Pilleron et al. 2023.[10] This could reflect real differences in long-term OS but could also be explained by other factors such as time-period effects, differences in censoring patterns, differences in subsequent treatment patterns, or differences in the distributions of unmeasured prognostic factors of OS across the two settings. In a post-hoc analysis, we found some indication of a time period effect with OS curves similar to when restricting US data to the period before the widespread use of immunotherapies in the US. The importance of the introduction of immunotherapies is evidenced in Snee et al. 2021, where we see higher survival over time for patients initiating therapy between 2013 and 2017 versus 2007 and 2012.[18]

While we showed good concordance for the UK and the US in 1L treatment for aNSCLC by drug class, the generalisability of these results to other countries, indications, lines of therapy, specific products, patient subgroups, or outcomes is unclear and should be explored further. Of note, a previous study in the same indication found OS results from the US were similar to OS results from Canada (Ramagopalan et al. 2022),[8] although with greater differences identified for 1L immunotherapy than for chemotherapy.

<sup>1</sup>/ 318

A key limitation of the study relates to the UK data used for comparison. First, the study included data from only nine sites and its representativeness to the general UK population is unknown. However, we found similar results for 1L chemotherapy when using aggregate data reported from the national SACT registry.[10] Second, we did not have access to full details of the study design

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in the original UK retrospective study, for instance, how combination therapies consisting of more than one drug class were considered in classifying 1L and 2L therapies (except for immunotherapy which was stated to be monotherapy only). Third, we only had aggregate data for comparison. This limited our ability to further adjust for patient characteristics or subsequent lines of therapy. Fourth, the UK data had access to only a limited set of demographic and clinical characteristics and the definitions did not always align with those from the US data. During the time of the study, there were differences between the countries in biomarker testing threshold scores for use of immunotherapy, though additional sensitivity analysis did not find this to meaningfully change the study results (see Supplementary Table 8). There may be additional prognostic variables for which adjustment could improve comparability of OS between the UK and US (Supplementary Tables 9–11). However, it is worth noting that despite these limitations we found OS results to be comparable between the UK and the US. Currently, with the limited availability of representative and clinically orientated local patient-level data sources, this is more likely to reflect the context in which such studies will be used to inform decision-making. Finally, it was not suitable to compare TTD, due to meaningful differences in the definitions used (Supplementary Table 12), which is an important outcome for health economic analyses. Future work should assess the transportability of TTD and other HTA relevant outcomes.

These results should help inform HTA reviewers when assessing the relevance of US data in the evaluation of aNSCLC therapies.

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**Contributors:** BA is responsible for the overall content as guarantor. BA and PJ were responsible for the conceptualization of the study. BA, PM, SK, BB, AS, and JK were involved in the development or design of methodology. PM and BB provided support for software, formal analysis, and resourcing. BB led validation of the study results. PM and BA conducted the investigation. PM prepared visualisations of the work. SK and PJ oversaw project administration. JK and AS provided supervision of the research activities. SK and PM wrote the original draft of the manuscript. PM and BB had full access to all data in the study. All authors contributed to writing and reviewing the manuscript and approved the submitted version. Acknowledgements: This research was presented, in part, at the ISPOR EU conference in November 2023 with the title, "Transportability of Overall Survival Estimates from US to UK Populations Receiving First-Line Treatment for Advanced Non-Small-Cell Lung Cancer." Publication management and editorial support was provided by Darren Johnson, PhD, an employee of Flatiron Health, Inc. Competing interests: At the time of this study, SK, PM, BB, TJR, BA, JK, and AS reported employment with Flatiron Health, Inc., which is an independent member of the Roche Group. BA conducted this work as an employee of Flatiron Health, Inc. PM, BB, TJR, BA, JK, and AS reported stock ownership in Roche. All other authors declared no competing interests. Funding: This study was sponsored by Flatiron Health, Inc.--an independent member of the Roche group. Flatiron Health, Inc. was involved in the writing of the manuscript and the decision to submit for publication. **Data availability statement:** The data that support the findings of this study were originated by and are the property of Flatiron Health, Inc., which has restrictions prohibiting the authors from 

making the data set publicly available. Requests for data sharing by license or by permission for the specific purpose of replicating results in this manuscript can be submitted to PublicationsDataAccess@flatiron.com. REFERENCES 1 National Institute for Health and Care Excellence. NICE real-world evidence framework. 2022. https://www.nice.org.uk/corporate/ecd9/chapter/overview (accessed 6 October 2023) 2 IQWiG. [A19-43] Development of scientific concepts for the generation of routine practice data and their analysis for the benefit assessment of drugs according to §35a Social Code Book V – rapid report. 2020. https://www.iqwig.de/en/projects/a19-43.html (accessed 6 October 2023) 3 Haute Autorité de santé. Real-world studies for the assessment of medicinal products and medical devices. 2021. https://www.has-sante.fr/upload/docs/application/pdf/2021-06/real-world studies for the assessment of medicinal products and medical devices.pdf (accessed 6 October 2023) 4 Kang J, Cairns J. Exploring uncertainty and use of real-world data in the National Institute for Health and Care Excellence single technology appraisals of targeted cancer therapy. BMC Cancer. 2022;22:1268. 5 Jaksa A, Arena PJ, Chan KKW, et al. Transferability of real-world data across borders for regulatory and health technology assessment decision-making. Front Med. 2022;9:1073678. 6 Dahabreh IJ, Robertson SE, Steingrimsson JA. Learning about treatment effects in a new target population under transportability assumptions for relative effect measures. arXiv 2202.11622 [Preprint]. February 23, 2022 https://doi.org/10.48550/arxiv.2202.11622 7 Degtiar I, Rose S. A Review of Generalizability and Transportability. Annu Rev Stat Appl. 2022;10:501-24. 8 Ramagopalan SV, Popat S, Gupta A, et al. Transportability of Overall Survival Estimates 

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430	
121	Figure 1. OS ourses for the UK and US before and after standardisation by 11. drug class
431	Figure 1. OS curves for the OK and OS before and after standardisation by TE drug class
432	US data standardised to reflect average characteristics of patients in the UK for age, sex, ECOG PS score
433	(0-1 or 2+), and histology (squamous cell, non-squamous cell, unknown). IO mono=immunotherapy
434	



Evaluating transportability of overall survival estimates from US to UK populations receiving first-line treatment for advanced non-small cell lung cancer: a retrospective cohort study

# SUPPLEMENTARY MATERIALS

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# Supplementary Table 1. Pragmatic literature review

Factor	Lester et al. (2021)	Snee et al. (2021)	Pilleron et al. (2023)
Peer-reviewed	Yes	Yes	No (Preprint)
Used in our analysis	Yes	No	Sensitivity analyses
Data Source	9 NHS Trusts and hospitals around the UK	Leeds Teaching hospitals	UK SACT dataset
Population of interest	Patients with stage IV advanced NSCLC	People with NSCLC	Patients with advanced NSCLC in Stages III and IV (analyses stratified by stage)
Sample Size	1003	3739	20,716
Treatment of interest	1L chemo, immunotherapy and targeted therapy	NA	Chemotherapy (Cytotoxic)
Index date anchor	1L treatment initiation	Disease diagnosis	1L treatment initiation
Study Period	2016–2019 (Enrol: 2016 to 2018)	2007–2018 (Enrol: 2007–2017)	2014–2018 (Enrol: 2014–2017)
Patient characteristics available at index	Age Sex ECOG PS Histology TNM Stage Biomarkers (high missingness)	Age Sex WHO performance status Histology TNM stage	Age Sex ECOG PS Ethnicity Treatment intent(curative vs palliative)
Death Ascertainment	Methodology not mentioned	Linkage of EMR to the Office of National Statistics death certificates	Linkage of SACT data to data from t National Cancer Registration and Analysis Service (NCRAS) data
OS Analysis	Whole cohort regardless of treatment Stratified by treatment	First stratified by disease stage(I, II, III, IV) Within each stage stratum, they stratified by tumour histology (squamous, nonsquamous,) and year of diagnosis	First stratified by disease stage (III vs IV) Within each stage stratum, they stratified by age (< 75 vs 75+)

**Search-term in pubmed**: (advanced non-small lung cancer OR aNSCLC OR advanced NSCLC OR metastatic non-small lung cancer OR met aNSCLC) AND (treatment pattern OR treatment guideline OR practice pattern OR treatment practice) AND (overall survival OR OS OR survival OR outcomes OR discontinuation OR ttd OR time on treatment OR ToT) AND (United Kingdom OR UK OR England). Filters applied: 2011 to 2022, Classical Article, Clinical Study, Comparative Study, Guideline, Meta-Analysis, Observational Study, Practice Guideline, Preprint, Review, Systematic Review. 1L=first-line. chemo=chemotherapy. ECOG PS=Eastern Cooperative Oncology Group performance status. EMR=electronic medical record. NA=not applicable.

NHS=National Health Service. NSCLC=non-small cell lung cancer. OS=overall survival. SACT=systemic anti-cancer therapy. WHO=World Health Organization.

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Supplementary Figure 1. Flow diagram of inclusion and exclusion criteria applied to the real-world cohort.

21 patients were excluded because their imputed death date preceded treatment start. In Flatiron Health date of death is provided at the month granularity for privacy reasons. For the analysis, the date of death is imputed to be the 15th of the month. 1L=first-line therapy. Chemo=chemotherapy. ECOG PS=Eastern Cooperative Oncology Group performance status. EHR=electronic health record. Immuno/IO=immunotherapy. Targeted=targeted therapy.

	Overall		1L Ch	emo	1L IO m	onotherapy	1 L targe	ted the rapy
Characteristic	UK (n=1003)	US (n=3819)	UK (n= 698)	US (n=2313)	UK (n = 179)	US (n=836)	UK (n = 126)	 of US (ኇ=ฏฏฏ
Proportion of study pop., %	100	100	69.6	60.6	17.8	21.9	12.6	nber 2 nseign es r <del>el</del> a
Median follow-up (range*), months	9.2 (0.0– 42.7)	9.0 (0.0– 42.9)	7.9 (0.0– 42.7)	7.3 (0.0– 42.9)	12.7 (0.1– 37.3)	8.1 (0.0–42.3)	16.3 (0.1– 37.1)	20.3 4 8 9 0
Median age(range*), years	68 (28– 93)	69 (21– 81)	68 (28–88)	69 (21– 81)	67 (48– 90)	71(38–81)	70 (32– 93)	textber 69 (25er)
Sex, n (%)								ided id da
Male	541 (53.9)	2013 (52.7)	395 (56.6)	1311 (56.7)	94 (52.5)	439 (52.5)	52 (41.3)	(AB0 263 m309.5) 263 mi
Female	462 (46.1)	1806 (47.3)	303 (43.4)	1002 (43.3)	85 (47.5)	397 (47.5)	74 (58.7)	
Tumour histology, n (%)	, , ,	<b>``</b>	. ,		, , ,	, <i>,</i> ,		òmjoper I trainir
Squamous	243 (24.2)	957 (25.1)	202 (28.9)	730 (31.6)	38 (21.2)	210 (25.1)	3 (2.4)	ي 17≩2.53.
Non-squamous	641(63.9)	2084 (70.3)	391 (56.0)	(63.1)	133(74.3)	584 (69.9)	117 (92.9)	640 <u>₹</u> 95.5)
Not specified	119 (11.9)	178 (4.7)	105 (15.0)	123 (5.3)	8 (4.5)	42 (5.0)	6 (4.8)	13∦51.9€
ECOG PS score, n (%)								ne 11, ; ;hnolo
0–1	759 (75.7)	2786 (73.0)	513 (73.5)	1714 (74.1)	157 (87.7)	556 (66.5)	89 (70.6)	<b>Gie</b> 202 516 (77.97)
2+	244 (24.3)	1033 (27.0)	185 (26.5)	599 (25.9)	22 (12.3)	280 (33.5)	37 (29.4)	154 (23.2)
Race/Ethnicity, No. (%)								nce Bib
Asian	••	117 (3.1)	••	35 (1.5)	••	17 (2.0)	••	65 (9.7 <b>8</b>

BMJ Open 5 Supplementary Table 2. Baseline characteristics and details of follow-up for patients in the UK and US by 1L drug class

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	Ove	erall	1L Chemo		1L IO monotherapy		1 L targeted th <del>≩</del> r	
Characteristic	UK (n=1003)	US (n=3819)	UK (n= 698)	US (n=2313)	UK (n = 179)	US (n=836)	UK (n = 126)	iudi US (jj
Black or African American	••	354 (9.3)	••	235 (10.2)	••	75 (9.0)		444se
White	••	(70.1)	••	(71.4)	••	608 (72.7)	••	419 <b>6</b>
Other Race	••	333 (8.7)	••	185 (8.0)	••	66 (7.9)		82 <b>(a</b>
Missing/Unknown <b>Practice Type, No.</b> (%)	••	337 (8.8)		207 (8.9)	••	70 (8.4)		60 <b>€ext</b> and d
Community	••	3241 (84.9)		1985 (85.8) 290	••	725 (86.7)		531 min
Academic	••	521 (13.6)	••	(12.5)	••	104 (12.4)	••	<b>آر</b> بھر 127
Both	••	57 (1.5)	••	38 (1.6)	••	7 (0.8)	••	12 A
Time from advanced diag. to treatment initiation (months)		1.15		1.15		1 25 (0 85		aining, and sin
Median (IQR) Smoking History, No. (%)	••	(0.76– 1.74)	••	1.68)	••	1.97)	7/	1.12 filter techn
History of smoking		3200 (83.8)	••	2095 (90.6)		765 (91.5)		ologies 340es
No history of smoking	••	610 (16.0)	••	213 (9.2)	••	70 (8.4)	••	327 (4
documented	••	9 (0.2)	••	5 (0.2)	••	1 (0.1)	••	3 (0
EGFR Status, No. (%)								
Mutation positive	108 (10.8)	556 (14 6)	1 (0 1)	65 (2.8)	0 (0 0)	11 (1 3)	107 (84 9)	480 (7

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	7	,	
1	1		

	Ove	rall	1L Chemo		1L IO monotherapy		1 L targeted the	
Characteristic	UK (n=1003)	US (n=3819)	UK (n= 698)	US (n=2313)	UK (n = 179)	US (n=836)	UK (n = 126)	US (te
Mutation negative		2078 (54.4)	••	1333 (57.6)	••	613 (73.3)		132 4 se
Unknown/Missing	••	1185 (31.0)	••	915 (39.6)	••	212 (25.4)	••	ій 58 <b>б</b> е
ALK Status, No. (%)								ated
Rearrangement present	19 (1.9)	97 (2.5)	0 (0.0)	8 (0.3)	0 (0.0)	5 (0.6)	19 (15.1)	5 84
Rearrangement not present	••	2332 (61.1)		1302 (56.3)		604 (72.2)		426 d
Unknown/Missing	••	1390 (36.4)		1003 (43.4)	••	227 (27.2)	••	ata 160 ₩
ROS1 Status, No. (%)								ning
Rearrangement present	••	33 (0.9)	••	8 (0.3)	••	1 (0.1)		ָ 24 <b>ב</b>
Rearrangement not present	••	1917 (50.2)	••	1024 (44.3)	••	504 (60.3)	••	inin 389
Unknown/Missing	••	1869 (48.9)	••	1281 (55.4)	••	331 (39.6)		and 257 ⊈
<i>PDL1</i> Status**, No. (%)								milar te
PD-L1 positive	182 (18.1)	1486 (38.9)	3 (0.4)	586 (25.3)	179 (100)	669 (80.0)	0 (0.0)	231 <b>ế</b>
PD-L1 negative/not detected	••	728 (19.1)	••	535 (23.1)	••	39 (4.7)		ogies 154 <u>%</u>
Unknown/Missing	••	1605 (42.0)	••	1192 (51.5)	••	128 (15.3)	••	285 (4
*Lester et al.,(2021) o	only reporte	d range. A	LK=anap	lastic lymp	homa kinas	se. chemo=ch	emotherap	y. ECC
PS=Eastern Coopera	tive Oncolo	ogy Group	performar	nce status.	EGFR=ep	idermal growt	h factor rec	ceptor.
Characteristic UK (n=3819) UK (n=058) UK (n=179) US (n=836) UK (n=126) US (n=1		Overall	1L Chemo	1L IO m	onotherapy	1 L targe	ਰ eted th∄	
---	------------------------	----------------------------	----------------------------	-----------------	------------------	-----------------	---------------	
IO=immunotherapy. ROS1=ROS proto-oncogene 1, receptor tyrosine kinase. PDL1/PD-L1=programme death ligand 1. **In the US analysis, patients were considered PD-L1 positive if the PD-L1 tumour proportion score was ≥ 1% or if there was reference to PD-L1 positivity in the medical chart.	Characteristic	UK US (n=1003) (n=3819)	UK (n= US 698) (n=2313)	UK (n = 179)	US (n=836)	UK (n = 126)		
death ligand 1. **In the US analysis, patients were considered PD-L1 positive if the PD-L1 tumour proportion score was ≥ 1% or if there was reference to PD-L1 positivity in the medical chart.	IO=immunotherapy.	ROS1=ROS proto-ond	cogene 1, receptor t	yrosine kina	ase. PDL1/PD	-L1=progra	amme	
score was ≥ 1% or if there was reference to PD-L1 positivity in the medical chart.	death ligand 1. **In t	he US analysis, patien	nts were considered	PD-L1 pos	itive if the PD-	L1 tumour	prop	
ed to text and data mining, Al training, and similar technol	score was ≥ 1% or it	f there was reference to	o PD-L1 positivity in	the medica	al chart.		relat	
							نة	

## Supplementary Table 3. Treatment switching from first to second line therapies in UK and US

		1L th	erapy	
	Any	Chemo	IO	Targeted
UK				
Any 2L	287 (29%)	229 (33%)	28 (16%)	30 (24%)
Conditional on 2L				
Chemo	104 (36%)	74 (32%)	26 (93%)	4(13%)
Ю	148 (52%)	146(64%)	2 (7%)	0 (0%)
Targeted	35 (12%)	9(4%)	0 (0%)	26 (87%)
US				
Any 2L	1835 (48%)	1245 (54%)	234 (28%)	356 (53%)
Conditional on 2L				
Chemo	330 (18%)	201 (16%)	105 (45%)	24 (7%)
10	896 (49%)	827 (66%)	38 (16%)	31 (9%)
Targeted	317 (17%)	65 (5%)	9 (4%)	243 (68%)
Other*	292 (16%)	152 (12%)	82 (35%)	58 (16%)

chemo=chemotherapy. IO=immunotherapy. 1L=first-line. 2L=second-line.

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### Supplementary Table 4. Overall survival and restricted mean survival time for the extended US cohort

Analysis	Summary	US unweighted	US weighted	UK
	mOS (95% CI)	9.86 (9.30–10.4)	9.23 (8.71–9.79)	9.5(8.8–10.7)
Overall (N=5106)	RSMT at:			
	12 months	7.92(0.06)	7.78(0.06)	8.24(0.13)
	24 months	12.11(0.13)	11.79(0.13)	12.01(0.27)
	mOS (95% CI)	7.89 (7.39–8.34)	7.46 (7.06–8.05)	8.1(7.4–8.9)
Chemo (N= 3340)	RSMT at:			
	12 months	7.45(0.08)	7.32(0.08)	7.69(0.16)
	24 months	10.83(0.15)	10.55(0.16)	10.50(0.3)
	mOS (95% CI)	9.63 (7.95–11.2)	13.4 (10.9–15.7)	14.0(10.7–20.6)
IO mono (N= 892)	RSMT at:			
IO mono. (N= 892)	12 months	7.57(0.16)	8.26(0.17)	8.79(0.31)
	24 months	12.11(0.33)	13.50(0.35)	14.23(0.69)
	mOS (95% CI)	23.1 (21.0–24.9)	20.0 (17.2–22.9)	20.2(16.0–30.5)
Targeted (N= 874)	RSMT at:			
	12 months	9.98(0.12)	9.67( 0.13)	9.77(0.34)
	24 months	16.92(0.29)	16.08(0.30)	16.30(0.77)
chemo=chemothera performance status. survival. RMST=res	apy. CI=confidence interva IO=immunotherapy. IO n tricted mean survival time	al. ECOG PS=Eastern ( nono=immunotherapy n e. se=standard error. Ta	Cooperative Oncol nonotherapy. mOS rgeted=targeted th	ogy Group S=median over nerapy.

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## Supplementary Table 5. Results for sensitivity analysis imputing missing ECOG PS scores

Scenario	Prevalence ECOG PS 0 or 1 after imputation (Before = 73%)	Unweighted mOS (95% CI)	Weighted mOS (95% CI)
Best (impute missing ECOG PS as 0 or 1)	78.3%	10.48 (9.89–11.04)	9.20 (8.71–9.86)
Worst (impute missing ECOG PS of 2 or more)	58.6%	10.48 (9.89–11.04)	10.32 (9.72–11.01)

US data standardised to reflect average characteristics of patients in the UK for age, sex, ECOG PS score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknown). CI=confidence interval. ECOG PS=Eastern Cooperative Oncology Group performance status. mOS=median overall survival.

## Supplementary Table 6. OS results for 1L chemotherapy for US data using UK data from Pilleron et al. 2021

Analysis	Variable	US unweighted	US weighted	UK (Pilleron et al.)
	mOS (95% CI)	7.9 (7.6–8.2)	8.1 (7.8–8.5)	7.7 (7.5–7.9)
Age < 75	Survival prob est. (%) at			
Age via	6 months	59 (58–60)	60 (58–61)	59.7 (58.7–60.6)
	12 months	37 (36–38)	38 (36–39)	33.2 (32.3–34.1)
	mOS (95% CI)	7.1 (6.8–7.7)	7.6 (7.0–8.4)	7.9 (7.5–8.2)
Age > 75	Survival prob est. (%) at			
//gc = / 0	6 months	56 (54–59)	58 (55–61)	60.4 (58.4–62.5)
	12 months	35 (33–37)	38 (35–41)	33.4 (31.5–35.4)

US data standardised to reflect average characteristics of patients in the UK for age, sex, ECOG PS score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknown). 1L=first-line. CI=confidence interval. ECOG PS=Eastern Cooperative Oncology Group performance status. mOS=median overall survival. OS=overall survival.

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## Supplementary Table 7. Time to treatment discontinuation (TTD) from US Flatiron data before and after standardisation by 1L drug class

		Media	n rwTTD (95% CI)	
Analysis	Overall	Chemo	Immuno	Targeted
US Unweighted	3.7 (3.5–3.8)	3.0 (2.9–3.0)	4.6 (4.0–6.0)	9.7 (9.0–10.9)
US Weighted	3.4 (3.2–3.6)	3.0 (2.8–3.0)	6.2 (4.8–7.4)	9.2 (8.5–10.2)

US data standardised to reflect average characteristics of patients in the UK for age, sex, ECOG score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknown). 1L=first-line. chemo=chemotherapy. CI=confidence interval. ECOG PS=Eastern Cooperative Oncology Group performance status. IO=immunotherapy. rwTTD=real-world time to treatment discontinuation. Targeted=targeted therapy.

Survival probability





# Supplementary Table 8. Transportability analysis for immunotherapy exposed cohort with tumour proportion score of $\geq$ 50%

Analysis	Summary	US PDL1 50+ unweighted U	JS PDL1 50+ weighted	UK
	mOS (95% CI)	11.6(10.0–14.9)	14.9 (11.7–18.9)	14.0 (10.7–20.6)
IO mono.	12 months RMST (se)	8.01 (0.19)	8.48 (0.19)	8.79 (0.31)
	24 months RMST (se)	13.12 (0.40)	14.03 (0.42)	14.23 (0.69)

US data standardised to reflect average characteristics of patients in the UK for age, sex, ECOG PS score (0–1 or 2+), and histology (squamous cell, non-squamous cell, unknown). CI=confidence interval. IO mono=immunotherapy monotherapy. mOS=median overall survival. RMST=restricted mean survival time. se=standard error.

		Full M	odel	Reduc	ed Model
Variable		Log(HR)	95% CI	Log(HR)	95% C
Sex					
Female		••	••	••	••
Male		0.23	0.16–0.31	0.25	0.17–0.3
Age at treatment initiation		0.01	0.00–0.01	0.01	0.00-0.0
Race					
White		••	••	••	••
Non-white		-0.08	-0.18–0.01	••	••
Missing/Unknown		0.12	-0.01–0.26	••	
Practice Type					
Community		- "	••	••	••
Academic		-0.10	-0.21–0.02	••	
Both		-0.80	-1.20.37	••	••
Time from diagnosis to treatment (months)	initiation	-0.03	-0.040.01	••	••
1L initiation year					
	2016	••	••	••	••
	2017	-0.03	-0.12–0.05	••	
	2018	-0.09	-0.22–0.04	••	
1L Regimen Class					
Chemo		••			
Immuno		-0.21	-0.310.11	-0.26	-0.350.
Targeted		-0.28	-0.480.07	-0.69	-0.800.9
ECOG PS					
0–1		••	••	••	••
2+		0.61	0.53–0.70	0.61	0.53–0.7
Tumor Pathology					
Squamous		••	••	••	••
Non-squamous		-0.13	-0.230.04	-0.19	-0.270.
Not otherwise specified		0.17	-0.01-0.36	0 14	-0.04-0 \$

### Supplementary Table 9. Full and reduced models for US for any 1L treatment

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	Full	Model	Reduce	d Model
Variable	Log(HR)	95% CI	Log(HR)	95% CI
Smoking History				
History of smoking	••	••	••	••
No history of smoking	-0.09	-0.22-0.03	••	••
Unknown/Not documented	1.30	0.58–2.1	••	••
EGFR Status				
Mutation positive	••	••	••	••
Mutation negative	0.38	0.17–0.60	••	••
Unknown/Missing	0.49	0.26-0.73	••	••
ALK Status				
Rearrangement present			••	••
Rearrangement not present	0.69	0.33–1.0	••	••
Unknown/Missing	0.53	0.16–0.91	••	••
ROS1 Status				
Rearrangement present			••	••
Rearrangement not present	0.50	-0.04–1.0	••	••
Unknown/Missing	0.64	0.09–1.2	••	••
PD-L1 Status				
PD-L1 positive	••	••	••	••
PD-L1 negative/not detected	0.15	-0.01–0.31		••
Unknown/Missing	0.07	-0.07–0.20		••
Likelihood-ratio test		chi-square(df=17	)= 90.3, p<0.001	
Concordance Index	0.	647	0.0	636
1L=first-line. ALK=anaplastic lyr ECOG PS=Eastern Cooperative growth factor receptor. HR=haz	nphoma kinase. c e Oncology Group ard ratio. Immuno: to-oncogene 1. re	hemo=chemothe performance sta =immunotherapy ceptor tyrosine k	erapy. CI=confi atus. EGFR=ep v. PD-L1=progr inase. Targete	dence inter bidermal cammed cel ed=targeted

### Supplementary Table 10. Full model for overall survival in the US by 1L drug class

	Ch	emo	Immun	otherapy	Targ	jeted
Variable	Log(HR)	95% CI	Log(HR)	95% CI	Log(HR)	95% CI
Sex						
Female	••	••	••	••	••	••
Male	0.23	0.13–0.32	0.29	0.11–0.46	0.22	0.00–0.44
Age at treatment initiation	0.00	0.00-0.01	0.00	-0.01–0.01	0.02	0.01–0.04
Race						
White		••	••	••	••	••
Non-white	-0.13	-0.250.01	-0.07	-0.29–0.15	0.13	-0.11–0.38
Missing/Unknown	0.13	-0.04-0.29	0.23	-0.07–0.52	0.03	-0.36–0.42
Practice Type						
Community			••	••	••	••
Academic	-0.02	-0.16–0.13	-0.37	-0.650.08	-0.11	-0.39–0.17
Both	-0.78	-1.30.28	-0.05	-1.0–0.95	-2.00	-4.00.05
Time from diagnosis to treatment initiation (months)	-0.04	-0.060.01	-0.02	-0.04–0.01	-0.04	-0.09–0.02
1L initiation year						
20	16 ••	- Č		••	••	••
20	17 -0.02	-0.12–0.09	-0.19	-0.45–0.06	-0.01	-0.240.22
20	18 -0.03	-0.18–0.13	-0.34	-0.670.02	-0.12	-0.50–0.25
ECOG PS						
0–1	••	••			••	••
2+	0.57	0.46-0.67	0.71	0.54–0.88	0.71	0.47–0.94
Tumor Pathology						
Squamous	••	••	••		••	••
Non-squamous	-0.06	-0.17–0.05	-0.31	-0.520.10	-0.64	-1.20.09
NOS	0.20	-0.02–0.41	-0.11	-0.51–0.29	0.34	-0.44–1.1
Smoking History						
History of smoking	••	••	••	••	••	••
No history of smoking	-0.03	-0.21–0.14	0.04	-0.26–0.35	-0.36	-0.580.14
Unknown/Not documented	1.90	0.87–2.9	0.53	-1.5–2.5	0.33	-1.1–1.7

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	Che	emo	Immun	otherapy	Targeted	
Variable	Log(HR)	95% CI	Log(HR)	95% CI	Log(HR)	95% CI
EGFR Status						
Mutation positive	••	••	••	••	••	••
Mutation negative	0.33	0.02–0.64	-0.86	-1.60.16	0.51	0.17–0.85
Unknown/Missing	0.40	0.05–0.74	-0.41	-1.1–0.31	0.63	0.23–1.0
ALK Status						
Rearrangement present	••	••	••	••	••	••
Rearrangement not present	0.69	-0.20–1.6	0.15	-1.0–1.3	0.65	0.19–1.1
Unknown/Missing	0.71	-0.19–1.6	-0.29	-1.5–0.94	0.68	0.17–1.2
PD-L1 Status						
PD-L1 positive	0.	••	••	••	••	••
PD-L1 negative/not detected	0.09	-0.12-0.30	0.31	-0.10–0.72	0.27	-0.21–0.76
Unknown/Missing	-0.03	-0.22-0.17	0.05	-0.16–0.26	0.44	-0.01–0.89
						20
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	0. C lymphoma k ncology Grou NOS=not othe	61 kinase. chemo p performanco erwise specifio	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor GFR=epiderm programmed	nfidence inte nal growth fa cell death lig	rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	0. c lymphoma k ncology Grou NOS=not othe	61 kinase. chemo p performanco erwise specifio	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor GFR=epiderm programmed	nfidence inte nal growth fa cell death lig	<sup>∞8</sup> rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	o. c lymphoma k ncology Grou NOS=not othe	61 kinase. chemo p performanco erwise specifio	0 o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor GFR=epiderm programmed	ofidence inte nal growth fa cell death lig	<sup>∞8</sup> rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	o. c lymphoma k hcology Grou NOS=not othe	61 kinase. chemo p performanco erwise specific	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor GFR=epiderm programmed	nfidence inte nal growth fa cell death lig	<sup>∞8</sup> rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	0. C lymphoma H hcology Grou NOS=not othe	61 kinase. chemo p performance erwise specifie	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor GFR=epiderm programmed	ofidence inte nal growth fa cell death lig	<sup>∞8</sup> rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	o. c lymphoma k hcology Grou NOS=not othe	61 kinase. chemo p performance erwise specifie	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor GFR=epiderm programmed	ofidence inte nal growth fa cell death lig	<sup>∞8</sup> rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	o. c lymphoma k hcology Grou NOS=not othe	61 kinase. chemo p performance erwise specific	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor GFR=epiderm programmed	nfidence inte nal growth fa cell death lig	<sup>∞8</sup> rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	0. c lymphoma k hcology Grou NOS=not othe	61 kinase. chemo p performance erwise specific	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor SFR=epiderm programmed	nfidence inte nal growth fa cell death lig	™ rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	0. c lymphoma k hcology Grou NOS=not othe	61 kinase. chemo p performance erwise specifie	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor SFR=epiderm programmed	nfidence inte nal growth fa cell death lig	™ rval. ECOG gand 1.
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	0. c lymphoma k hcology Grou NOS=not othe	61 kinase. chemo p performance erwise specifie	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor GFR=epiderm programmed	nfidence intenal growth fa cell death lig	rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	0. c lymphoma H hcology Grou NOS=not othe	61 kinase. chemo p performance erwise specifie	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor GFR=epiderm programmed	nfidence intenal growth fa cell death lig	rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	0. c lymphoma k hcology Grou NOS=not othe	61 kinase. chemo p performance erwise specifie	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor GFR=epiderm programmed	nfidence inte nal growth fa cell death lig	<sup>∞8</sup> rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	o. c lymphoma k hcology Grou NOS=not othe	61 kinase. chemo p performance erwise specifie	o p=chemothe e status. EC ed. PD-L1=	erapy. CI=cor SFR=epiderm programmed	nfidence inte nal growth fa cell death lig	rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	o. c lymphoma k hcology Grou NOS=not othe	61 kinase. chemo p performance erwise specifie	o p=chemothe e status. EC ed. PD-L1=	erapy. CI=cor SFR=epiderm programmed	nfidence intenal growth fa cell death lig	rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	o. c lymphoma k hcology Grou NOS=not othe	61 kinase. chemo p performance erwise specifie	o p=chemothe e status. EC ed. PD-L1=	erapy. CI=cor SFR=epiderm programmed	nfidence intenal growth fa cell death lig	rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	o. c lymphoma H hcology Group NOS=not othe	61 kinase. chemo p performance erwise specifie	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor SFR=epiderm programmed	nfidence intenal growth fa cell death lig	rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	o. c lymphoma k hoology Grou NOS=not othe	61 kinase. chemo p performance erwise specifie	o=chemothe e status. EC ed. PD-L1=	erapy. CI=cor SFR=epiderm programmed	nfidence intenal growth fa cell death lig	rval. ECOG ctor gand 1.
Concordance Index 1L=first-line. ALK=anaplastic PS=Eastern Cooperative Or receptor. HR=hazard ratio. N Targeted=targeted therapy.	o. c lymphoma k hoology Grou NOS=not othe	61 kinase. chemo p performance erwise specifie	o p=chemothe e status. EC ed. PD-L1=	erapy. CI=cor SFR=epiderm programmed	nfidence intenal growth fa cell death lig	rval. ECOG ctor gand 1.

	Ch	emo	Imm	iuno	Tar	geted
Variable	Log(HR)	95% CI	Log(HR)	95% CI	Log(HR)	
Sex						
Female	••	••	••	••	••	••
Male	0.24	0.14–0.33	0.26	0.09–0.43	0.29	0.08–0.5 <sup>,</sup>
Age at treatment initiation	0.00	0.00–0.01	0.01	0.00–0.01	0.03	0.02-0.04
ECOG PS						
0–1		••	••	••	••	••
2+	0.57	0.47–0.68	0.68	0.51–0.85	0.64	0.41–0.87
Tumor Pathology						
Squamous			••	••	••	••
Non-squamous	-0.12	-0.220.02	-0.33	-0.510.14	-0.84	-1.40.29
NOS	0.18	-0.04–0.39	-0.15	-0.54–0.24	0.24	-0.53–1.0
Concordance Index	0	.59	0.	63	0	.65
Immuno=immunotherapy. Targeted=targeted therap	NOS=not othe y.	erwise specific	ed. PD-L1=p	rogrammed c	ell death lig	and 1.

## Supplementary Table 12. The difference in the definition of rwTTD in the US and UK analyses

	Definition of Endpoint in data source	
Endpoint	Flatiron Health	Lester et al. 2021
rwTTD	Time from 1L treatment initiation to treatment discontinuation (for any reason including death). Start date: first drug episode for the drug of interest within a given line of therapy (LOT) End date: last drug episode for the drug of interest within a given LOT Time at risk is time elapsed between start and end dates of a LOT A patient is treated as uncensored if ANY of the following three events are observed in the data: The patient advanced to a new LOT. Because rwTTD is defined within a given LOT, evidence of advancement to a new LOT mandates the discontinuation of the treatment offered under the preceding line. The patient has not advanced to a new LOT, but has a recorded date of death. Mortality should be treated as confirmatory of treatment discontinuation. The patient has not advanced to a new LOT and has no recorded date of death, but has sufficient evidence of confirmed structured activity after the last drug episode for the drug(s) of interest. In the absence of a more definitive condition like LOT advancement or evidence of death, inference of treatment discontinuation from structured EHR data is necessary. A prolonged period (e.g., 120 days) of confirmed structured activity following the last recorded drug episode may be considered reasonable evidence of treatment discontinuation because it suggests that the patient is still being followed at the treating clinic; thus, one can assume consistent capture of treatment data. As such, it is unlikely that the cessation of new drug episodes is the result of missing data.	Time from 1L treatment initiation to treatment discontinuation (for any reason including death). ["in patients who discontinued treatment but were still alive, the treatment end date was recorded as the start date of the last treatment cycle was not available, and the last cycle start date was the latest date when it was certain that treatment was continuing."]

1L=first-line therapy. EHR=electronic health records. LOT=line of therapy. rwTTD= real-world time to treatment discontinuation.